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 NEWS  23 JUN 20  MEDICONF to be removed from STN

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=> s 303184-53-4
L1          13 303184-53-4

=> d l1 1-13 ibib abs kwic

L1   ANSWER 1 OF 13  BIOSIS  COPYRIGHT (c) 2005 The Thomson Corporation  on STN
ACCESSION NUMBER:    2003:285955  BIOSIS
DOCUMENT NUMBER:     PREV200300285955
TITLE:               Characterization of in vitro biotransformation of new,
                     orally active, direct thrombin inhibitor ximelagatran, an
                     amidoxime and ester prodrug.
AUTHOR(S):           Clement, Bernd [Reprint Author]; Lopian, Katrin
```

CORPORATE SOURCE: Pharmazeutisches Institut, Gutenbergstrasse 76, D-24118, Kiel, Germany
bclement@pharmazie.uni-kiel.de
SOURCE: Drug Metabolism and Disposition, (May 2003) Vol. 31, No. 5, pp. 645-651. print.
ISSN: 0090-9556 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jun 2003
Last Updated on STN: 19 Jun 2003

AB N-Hydroxylated amidines (amidoximes) can be used as prodrugs of amidines. The prodrug principle was developed in our laboratory for pentamidine and had been applied to several other drug candidates. One of these compounds is melagatran, a novel, synthetic, low molecular weight, direct thrombin inhibitor. To increase the poor oral bioavailability due to its strong basic amidine functionality selected to fit the arginine side pocket of thrombin, the less basic N-hydroxylated amidine was used in addition to an ethyl ester-protecting residue. The objective of this investigation was to study the reduction and the hydrolytic metabolism of ximelagatran via two mono-prodrugs (N-hydroxy-melagatran and ethyl-melagatran) to melagatran by in vitro experiments. New high-performance liquid chromatography methods were developed to analyze all four compounds. The biotransformation of ximelagatran to melagatran involving the reduction of the amidoxime function and the ester cleavage could be demonstrated in vitro by microsomes and mitochondria from liver and kidney of pig and human, and the kinetic parameters were determined. So far, one enzyme system capable of reducing N-hydroxylated structures has been identified in pig liver microsomes, consisting of cytochrome b5, NADH-cytochrome b5 reductase, and a P450 isoenzyme of the subfamily 2D. This enzyme system also reduces ximelagatran and N-hydroxy-melagatran. The participation of recombinant human CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6, and 3A4 with cytochrome b5 and b5 reductase in the reduction can be excluded. In summary, ximelagatran and N-hydroxy-melagatran are easily reduced by several enzyme systems located in microsomes and mitochondria of different organs.

RN . . . (cytochrome P450 2C9)
329978-01-0 (CYP2C9)
330597-62-1 (cytochrome P450 2D6)
330597-62-1 (CYP2D6)
329736-03-0 (cytochrome P450 3A4)
329736-03-0 (CYP3A4)
9035-39-6 (cytochrome b-5)
303184-53-4 (ethyl-melagatran)
159776-70-2 (melagatran)
9002-04-4 (thrombin)
9002-04-4 (EC 3.4.21.5)
192939-46-1 (ximelagatran)

L1 ANSWER 2 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:113535 BIOSIS
DOCUMENT NUMBER: PREV200300113535
TITLE: Determination of ximelagatran, an oral direct thrombin inhibitor, its active metabolite melagatran, and the intermediate metabolites, in biological samples by liquid chromatography-mass spectrometry.
AUTHOR(S): Larsson, Marita [Reprint Author]; Ahnoff, Martin; Abrahamsson, Anna; Logren, Ulrika; Fakt, Christina; Ohrman, Irene; Persson, Bengt-Arne
CORPORATE SOURCE: DMPK and Bioanalytical Chemistry, AstraZeneca R and D Molndal, S-431 83, Molndal, Sweden
marita.s.larsson@astrazeneca.com
SOURCE: Journal of Chromatography B, (15 January 2003) Vol. 783, No. 2, pp. 335-347. print.
ISSN: 1570-0232 (ISSN print).
DOCUMENT TYPE: Article

LANGUAGE: English
ENTRY DATE: Entered STN: 26 Feb 2003
Last Updated on STN: 26 Feb 2003

AB Analytical methods for the determination of ximelagatran, an oral direct thrombin inhibitor, its active metabolite melagatran, and intermediate metabolites, melagatran hydroxyamidine and melagatran ethyl ester, in biological samples by liquid chromatography (LC) positive electrospray ionization mass spectrometry (MS) using selected reaction monitoring are described. Isolation from human plasma was achieved by solid-phase extraction on octylsilica. Analytes and isotope-labelled internal standards were separated by LC utilising a C18 analytical column and a mobile phase comprising acetonitrile-4 mmol/l ammonium acetate (35:65, v/v) containing 0.1% formic acid, at a flow-rate of 0.75 ml/min. Absolute recovery was apprx80% for ximelagatran, apprx60% for melagatran ethyl ester and >90% for melagatran and melagatran hydroxyamidine. Limit of quantification was 10 nmol/l, with a relative standard deviation <20% for each analyte and <5% above 100 nmol/l. Procedures for determination of these analytes in human urine and breast milk, plus whole blood from rat and mouse are also described.

RN 159776-70-2 (melagatran)
303184-53-4 (melagatran ethyl ester)
192939-72-3 (melagatran hydroxyamidine)
9002-04-4 (thrombin)
9002-04-4 (EC 3.4.21.5)
192939-46-1 (ximelagatran)

L1 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:304716 CAPLUS
DOCUMENT NUMBER: 142:62413
TITLE: Bioequivalence of ximelagatran, an oral direct thrombin inhibitor, as whole or crushed tablets or dissolved formulation
AUTHOR(S): Schuetzer, Kajs-Marie; Wall, Ulrika; Loennerstedt, Carina; Ohlsson, Lis; Teng, Renli; Sarich, Troy C.; Eriksson, Ulf G.
CORPORATE SOURCE: R+D Moelndal, AstraZeneca, Moelndal, Swed.
SOURCE: Current Medical Research and Opinion (2004), 20(3), 325-331
CODEN: CMROCX; ISSN: 0300-7995
PUBLISHER: LibraPharm Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: To investigate whether crushed or dissolved tablets of the oral direct thrombin inhibitor ximelagatran are bioequivalent to whole tablet administration. Ximelagatran is currently under development for the prevention and treatment of thromboembolic disorders. Research design and methods: This was an open-label, randomized, three-period, three-treatment crossover study in which 40 healthy volunteers (aged 20-33 yr) received a single 36-mg dose of ximelagatran administered in three different ways: I swallowed whole, II crushed, mixed with applesauce and ingested and III dissolved in water and administered via nasogastric tube. Results: The plasma concns. of ximelagatran, its intermediates and the active form melagatran were determined Ximelagatran was rapidly absorbed and the bioavailability of melagatran was similar after the three different administrations, fulfilling the criteria for bioequivalence. The mean area under the plasma concentration-vs.-time curve (AUC) of melagatran was 1.6 μmol·h/L (ratio 1.01 for treatment II/I and 0.97 for treatment III/I), the mean peak concentration (Cmax) was 0.3 μmol/L (ratio 1.04 for treatment II/I and 1.02 for treatment III/I) and the mean half-life (t1/2) was 2.8h for all treatments. The time to Cmax (tmax) was 2.2 h for the whole tablet and approx. 0.5 h earlier when the tablet was crushed or dissolved (1.7-1.8 h), due to a more rapid absorption. The study drug was well tolerated as judged from the low incidence and type of adverse events reported. Conclusion: The present study showed that the pharmacokinetics (AUC and Cmax) of melagatran were not significantly altered whether

ximelagatran was given orally as a crushed tablet mixed with applesauce or dissolved in water and given via nasogastric tube.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 159776-70-2, Melagatran 192939-72-3 **303184-53-4**, Ethyl melagatran
RL: BSU (Biological study, unclassified); BIOL (Biological study) (bioequivalence of ximelagatran as whole or crushed tablets or dissolved formulation)

L1 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:701571 CAPLUS
DOCUMENT NUMBER: 140:138746
TITLE: Ximelagatran, an oral direct thrombin inhibitor, has a low potential for cytochrome P450-mediated drug-drug interactions
AUTHOR(S): Bredberg, Eva; Andersson, Tommy B.; Frison, Lars; Thuresson, Annelie; Johansson, Susanne; Eriksson-Lepkowska, Maria; Larsson, Marita; Eriksson, Ulf G.
CORPORATE SOURCE: AstraZeneca R and D, Moelndal, Swed.
SOURCE: Clinical Pharmacokinetics (2003), 42(8), 765-777
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Ximelagatran is an oral direct thrombin inhibitor currently in clin. development for the prevention and treatment of thromboembolic disorders. After oral administration, ximelagatran is rapidly absorbed and extensively bioconverted, via two intermediates (ethyl-melagatran and hydroxy-melagatran), to its active form, melagatran. In vitro studies have shown no evidence for involvement of cytochrome P 450 (CYP) enzymes in either the bioactivation or the elimination of melagatran. Objective: To investigate the potential of ximelagatran, the intermediates ethyl-melagatran and hydroxy-melagatran, and melagatran to inhibit the CYP system in vitro and in vivo, and the influence of three CYP substrates on the pharmacokinetics of melagatran in vivo. Methods: The CYP inhibitory properties of ximelagatran, the intermediates and melagatran were tested in vitro by two different methods, using heterologously expressed enzymes or human liver microsomes. Diclofenac (CYP2C9), diazepam (CYP2C19) and nifedipine (CYP3A4) were chosen for coadministration with ximelagatran in healthy volunteers. Subjects received oral ximelagatran 24 mg and/or diclofenac 50 mg, a 10-min i.v. infusion of diazepam 0.1 mg/kg, or nifedipine 60 mg. The plasma pharmacokinetics of melagatran, diclofenac, diazepam, N-desmethyl-diazepam and nifedipine were determined when administered alone and in combination with ximelagatran. Results: No inhibition, or only minor inhibition, of CYP enzymes by ximelagatran, the intermediates or melagatran was shown in the in vitro studies, suggesting that ximelagatran would not cause CYP-mediated drug-drug interactions in vivo. This result was confirmed in the clin. studies. There were no statistically significant differences in the pharmacokinetics of diclofenac, diazepam and nifedipine on coadministration with ximelagatran. Moreover, there were no statistically significant differences in the pharmacokinetics of melagatran when ximelagatran was administered alone or in combination with diclofenac, diazepam or nifedipine. Conclusion: As ximelagatran did not exert a significant effect on the hepatic CYP isoenzymes responsible for the metabolism of diclofenac, diazepam and nifedipine, it is reasonable to expect that it would have no effect on the metabolism of other drugs metabolized by these isoenzymes. Furthermore, the pharmacokinetics of melagatran after oral administration of ximelagatran are not expected to be altered by inhibition or induction of CYP2C9, CYP2C19 or CYP3A4. Together, the in vitro and in vivo studies indicate that metabolic drug-drug interactions involving the major human CYP enzymes should not be expected with ximelagatran.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 159776-70-2, Melagatran 192939-46-1, Ximelagatran 192939-72-3
303184-53-4, Ethyl-melagatran
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); BIOL (Biological study)
(oral direct thrombin inhibitor ximelagatran has low potential for cytochrome P 450-mediated drug-drug interactions in vitro and in vivo in humans)

L1 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:701570 CAPLUS
DOCUMENT NUMBER: 139:270230
TITLE: No influence of mild-to-moderate hepatic impairment on the pharmacokinetics and pharmacodynamics of ximelagatran, an oral direct thrombin inhibitor
AUTHOR(S): Wahlander, Karin; Eriksson-Lepkowska, Maria; Frison, Lars; Fager, Gunnar; Eriksson, Ulf G.
CORPORATE SOURCE: AstraZeneca R and D, Moelndal, Swed.
SOURCE: Clinical Pharmacokinetics (2003), 42(8), 755-764
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: The oral direct thrombin inhibitor ximelagatran is a new class of anticoagulant currently in clin. development for the prevention and treatment of thromboembolic disease. After oral administration, ximelagatran is rapidly absorbed and bioconverted to its active form melagatran. Objective: To investigate the influence of mild-to-moderate hepatic impairment on the pharmacokinetic and pharmacodynamic properties of ximelagatran. Study design: Nonblinded, nonrandomised study. Participants: Twelve volunteers with mild-to-moderate hepatic impairment (classified as Child-Pugh A or B) and 12 age-, weight-, and sex-matched control volunteers with normal hepatic function. Methods: Volunteers received a single oral dose of ximelagatran 24mg. Plasma and urine samples were collected for pharmacokinetic and pharmacodynamic analyses. Results: The absorption and bioconversion of ximelagatran to melagatran were rapid in both groups. The maximum plasma concentration of melagatran (Cmax) was achieved 2-3 h after administration; the mean elimination half-life (t1/2z) was 3.6 h for hepatically impaired volunteers and 3.1 h for the control volunteers. The area under the plasma concentration-time curve (AUC) and Cmax of melagatran in volunteers with hepatic impairment were 11 and 25% lower than in control volunteers, resp. However, after correcting for the higher renal function (i.e. higher calculated creatinine clearance) in the hepatically impaired volunteers, the ratio of melagatran AUC for hepatically impaired/control volunteers was 0.98 (90% CI 0.80, 1.22), suggesting that mild-to-moderate hepatic impairment had no influence on the pharmacokinetics of ximelagatran. Melagatran was the predominant compound in urine, accounting for 13-14% of the ximelagatran dose. Renal clearance of melagatran was 13% higher in hepatically impaired than in control volunteers. There were no significant differences between the two groups in the concentration-response relation between plasma melagatran concentration and activated partial thromboplastin time (APTT). Baseline prothrombin time (PT) was slightly longer in the hepatically impaired patients than in the control volunteers, probably reflecting a slight decrease in the activity of coagulation factors. However, when concns. of melagatran were at their peak, the increase in PT from baseline values was the same in both groups. Capillary bleeding time was measured in the hepatically impaired patients only, and was not increased by ximelagatran. Ximelagatran was well tolerated in both groups. Conclusion: There were no differences in the pharmacokinetic or pharmacodynamic properties of melagatran following oral administration of ximelagatran between the hepatically impaired and control volunteers. These findings suggest that

dose adjustment for patients with mild-to-moderate impairment of hepatic function is not necessary.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 159776-70-2, Melagatran 192939-46-1, Exanta 192939-72-3, Melagatran hydroxyamidine **303184-53-4**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(no influence of mild-to-moderate hepatic impairment on pharmacokinetics and pharmacodynamics of ximelagatran (Exanta))

L1 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:497014 CAPLUS
DOCUMENT NUMBER: 139:390673
TITLE: No influence of obesity on the pharmacokinetics and pharmacodynamics of melagatran, the active form of the oral direct thrombin inhibitor ximelagatran
AUTHOR(S): Sarich, Troy C.; Teng, Renli; Peters, Gary R.; Wollbratt, Maria; Homolka, Robert; Svensson, Mia; Eriksson, Ulf G.
CORPORATE SOURCE: AstraZeneca LP, Wilmington, DE, USA
SOURCE: Clinical Pharmacokinetics (2003), 42(5), 485-492
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Ximelagatran, an oral direct thrombin inhibitor, is currently in clin. development for the prevention and treatment of thromboembolic disease. Following oral administration, ximelagatran undergoes rapid bioconversion to its active form, melagatran, via two minor intermediates. Obesity, defined as body mass index (BMI) >30 kg/m2, is a recognized risk factor for thrombosis. There is potential for differences in the pharmacokinetics and pharmacodynamics of drugs administered to obese vs. non-obese patients, and some drugs may require alternative administration strategies in obese patients. Objective: To investigate the effect of obesity on the pharmacokinetics and pharmacodynamics of melagatran after oral administration of ximelagatran. Design and participants: This was an open-label, single-dose, group-matched study in which obese subjects (BMI 32-39 kg/m2; six male and six female; age 21-40 yr) were matched by sex and age (±2 yr) with non-obese subjects (BMI 21-26 kg/m2; six male and six female; aged 21-39 yr). Each subject received a single oral dose of ximelagatran 24mg. Blood samples for determination of plasma concns. of melagatran and activated partial thromboplastin times (APTT; a marker of melagatran pharmacodynamics) were collected up to 12 h after administration. Results: There were no statistically significant differences in the pharmacokinetic properties of melagatran between obese and non-obese subjects. Values of area under the melagatran plasma concentration-time curve, maximum plasma concentration, (Cmax), time at which Cmax occurred and terminal elimination half-life were approx. 1 μmol • h/L, 0.2 μmol/L, 2 h and 3 h in both obese and non-obese subjects, resp. In addition, there was no statistically significant difference between the obese and non-obese subjects in the amount of ximelagatran, melagatran or the minor intermediates ethyl-melagatran and melagatran hydroxyamidine excreted in urine. When relating the prolongation of APTT ratio to the square root of plasma concentration of melagatran and obesity status (no/yes), no statistically significant interaction between plasma concentration and obesity status was observed Ximelagatran was well tolerated in both obese and non-obese subjects, and no bleeding events or serious adverse events occurred. Conclusion: No differences in the pharmacokinetics or pharmacodynamics of melagatran were detected between obese and non-obese subjects after oral administration of ximelagatran, suggesting that dose adjustment of ximelagatran in obesity (BMI up to 39 kg/m2) is not

necessary.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 192939-72-3, Melagatran hydroxyamidine **303184-53-4**, Ethyl melagatran
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(influence of obesity on the pharmacokinetics and pharmacodynamics of melagatran)

L1 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:497013 CAPLUS
DOCUMENT NUMBER: 139:390672
TITLE: No influence of ethnic origin on the pharmacokinetics and pharmacodynamics of melagatran following oral administration of ximelagatran, a novel oral direct thrombin inhibitor, to healthy male volunteers
AUTHOR(S): Johansson, Linda C.; Andersson, Magnus; Fager, Gunnar; Gustafsson, David; Eriksson, Ulf G.
CORPORATE SOURCE: AstraZeneca R&D, Moelndal, Swed.
SOURCE: Clinical Pharmacokinetics (2003), 42(5), 475-484
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To determine the influence of ethnic origin on the pharmacokinetic and pharmacodynamic properties of melagatran after oral administration of ximelagatran, a novel oral direct thrombin inhibitor. Study design: This was an open-label, non-randomized study with a single study session. Subjects: Thirty-six young healthy male subjects living in France were divided equally according to their ethnic origin (African, Asian and Caucasian). Methods: All subjects received a single 50mg oral dose of ximelagatran in solution Blood and urine samples for pharmacokinetic evaluation were collected up to 12 and 24 h after administration, resp. Blood samples were also collected to determine the activated partial thromboplastin time (APTT), an ex vivo coagulation time measurement used to demonstrate inhibition of thrombin, up to 24 h after administration. Results: The absorption of ximelagatran, and its bioconversion to melagatran, was rapid in all three ethnic groups. The metabolite pattern in plasma and urine was similar in all groups, with melagatran being the dominant compound For ximelagatran, the mean area under the plasma concentration-time curve (AUC) was similar in the three groups, suggesting that there was no difference in the extent to which ximelagatran was absorbed. Melagatran AUC was higher in the Asian subjects, with a mean Asian/Caucasian ratio (95% CI) of 1.23 (1.04, 1.45). This was presumably because of their lower bodyweight, which is correlated to lower renal function. Following normalization for bodyweight, there were no statistically significant differences between the three ethnic groups. This finding suggests that renal elimination was lower for Asian subjects, whereas there were no differences in the conversion of ximelagatran to melagatran. The interindividual variability of melagatran AUC was low (coefficient of variation 19-26%), and the mean bioavailability of melagatran, estimated using a mean value for melagatran clearance obtained from Caucasian subjects in a previous study, was approx. 20% in all groups (range of mean values 19-23%). APTT increased nonlinearly with increasing melagatran plasma concentration, and no difference in the concentration-response relationship was
observed between the groups. Conclusion: After oral administration of ximelagatran, the pharmacokinetic and pharmacodynamic properties of melagatran are independent of ethnic origin. The elimination of melagatran is correlated with renal function.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 192939-72-3, Melagatran hydroxyamidine **303184-53-4**, Ethyl melagatran
RL: PKT (Pharmacokinetics); BIOL (Biological study)

(influence of ethnic origin on the pharmacokinetics and pharmacodynamics of melagatran following oral administration of ximelagatran to healthy male volunteers)

L1 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:334914 CAPLUS
DOCUMENT NUMBER: 138:348712
TITLE: A combination product comprising melagatran and dexamethasone
INVENTOR(S): Elg, Margareta
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035079	A1	20030501	WO 2002-SE1938	20021024
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2464085	AA	20030501	CA 2002-2464085	20021024
EP 1441738	A1	20040804	EP 2002-802081	20021024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013311	A	20041013	BR 2002-13311	20021024
JP 2005511544	T2	20050428	JP 2003-537646	20021024
ZA 2004003094	A	20050125	ZA 2004-3094	20040422
US 2005014701	A1	20050120	US 2004-493625	20040423
PRIORITY APPLN. INFO.:			SE 2001-3590 A	20011026
			WO 2002-SE1938 W	20021024

OTHER SOURCE(S): MARPAT 138:348712
AB There is provided a combination product comprising; (A) melagatran or a pharmaceutically acceptable derivative; and (B) dexamethasone or a pharmaceutically acceptable derivative thereof, wherein each of components (A) and (B) is formulated in admixt. with a pharmaceutically-acceptable adjuvant, diluent or carrier, as well as the use of such a combination product in the treatment of conditions including disseminated intravascular coagulation. Of the agents employed, only a combination of melagatran and dexamethasone completely protected rats from the development of disseminated intravascular coagulation.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT **303184-53-4**, Glycine, N-[(1R)-2-[(2S)-2-[[[[4-(aminoiminomethyl)phenyl]methyl]amino]carbonyl]-1-azetidinyl]-1-cyclohexyl-2-oxoethyl]-, ethyl ester 303184-54-5, Glycine, N-[(1R)-2-[(2S)-2-[[[[4-(aminoiminomethyl)phenyl]methyl]amino]carbonyl]-1-azetidinyl]-1-cyclohexyl-2-oxoethyl]-, methyl ester 303184-55-6, Glycine, N-[(1R)-2-[(2S)-2-[[[[4-(aminoiminomethyl)phenyl]methyl]amino]carbonyl]-1-azetidinyl]-1-cyclohexyl-2-oxoethyl]-, propyl ester 518287-81-5 518287-82-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination product comprising melagatran and dexamethasone)

L1 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:325363 CAPLUS

DOCUMENT NUMBER: 139:270214
TITLE: Characterization of in vitro biotransformation of new, orally active, direct thrombin inhibitor ximelagatran, an amidoxime and ester prodrug
AUTHOR(S): Clement, Bernd; Lopian, Katrin
CORPORATE SOURCE: Pharmaceutical Institute, Christian-Albrechts-University of Kiel, Kiel, Germany
SOURCE: Drug Metabolism and Disposition (2003), 31(5), 645-651
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB N-Hydroxylated amidines (amidoximes) can be used as prodrugs of amidines. The prodrug principle was developed in our laboratory for pentamidine and had been applied to several other drug candidates. One of these compds. is melagatran, a novel, synthetic, low mol. weight, direct thrombin inhibitor. To increase the poor oral bioavailability due to its strong basic amidine functionality selected to fit the arginine side pocket of thrombin, the less basic N-hydroxylated amidine was used in addition to an Et ester-protecting residue. The objective of this investigation was to study the reduction and the hydrolytic metabolism of ximelagatran via two mono-prodrugs (N-hydroxy-melagatran and ethyl-melagatran) to melagatran by in vitro expts. New high-performance liquid chromatog. methods were developed to analyze all four compds. The biotransformation of ximelagatran to melagatran involving the reduction of the amidoxime function and the ester cleavage could be demonstrated in vitro by microsomes and mitochondria from liver and kidney of pig and human, and the kinetic parameters were determined So far, one enzyme system capable of reducing N-hydroxylated structures has been identified in pig liver microsomes, consisting of cytochrome b5, NADH-cytochrome b5 reductase, and a P 450 isoenzyme of the subfamily 2D. This enzyme system also reduces ximelagatran and N-hydroxy-melagatran. The participation of recombinant human CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6, and 3A4 with cytochrome b5 and b5 reductase in the reduction can be excluded. In summary, ximelagatran and N-hydroxy-melagatran are easily reduced by several enzyme systems located in microsomes and mitochondria of different organs.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 159776-70-2, Melagatran 192939-46-1, Ximelagatran 192939-72-3, N-Hydroxymelagatran **303184-53-4**, Ethyl melagatran
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(in vitro biotransformation of ximelagatran, an amidoxime and ester prodrug, and role of microsomal and mitochondrial enzymes)

L1 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:156659 CAPLUS
DOCUMENT NUMBER: 139:223644
TITLE: Absorption, distribution, metabolism, and excretion of ximelagatran, an oral direct thrombin inhibitor, in rats, dogs, and humans
AUTHOR(S): Eriksson, Ulf G.; Bredberg, Ulf; Hoffmann, Kurt-Jurgen; Thuresson, Anneli; Gabrielsson, Margareth; Ericsson, Hans; Ahnoff, Martin; Gislen, Kristina; Fager, Gunnar; Gustafsson, David
CORPORATE SOURCE: AstraZeneca R and D Molndal, Moelndal, S-431 83, Swed.
SOURCE: Drug Metabolism and Disposition (2003), 31(3), 294-305
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The absorption, metabolism, and excretion of the oral direct thrombin inhibitor, ximelagatran, and its active form, melagatran, were sep. investigated in rats, dogs, and healthy male human subjects after

administration of oral and i.v. single doses. Ximelagatran was rapidly absorbed and metabolized following oral administration, with melagatran as the predominant compound in plasma. Two intermediates (ethyl-melagatran and OH-melagatran) that were subsequently metabolized to melagatran were also identified in plasma and were rapidly eliminated. Melagatran given i.v. had relatively low plasma clearance, small volume of distribution, and short elimination half-life. The oral absorption of melagatran was low and highly variable. It was primarily renally cleared, and the renal clearance agreed well with the glomerular filtration rate. Ximelagatran was extensively metabolized, and only trace amts. were renally excreted. Melagatran was the major compound in urine and feces after administration of ximelagatran. Appreciable quantities of ethyl-melagatran were also recovered in rat, dog, and human feces after oral administration, suggesting reduction of the hydroxyamidine group of ximelagatran in the gastrointestinal tract, as demonstrated when ximelagatran was incubated with feces homogenate. Polar metabolites in urine and feces (all species) accounted for a relatively small fraction of the dose. The bioavailability of melagatran following oral administration of ximelagatran was 5 to 10% in rats, 10 to 50% in dogs, and about 20% in humans, with low between-subject variation. The fraction of ximelagatran absorbed was at least 40 to 70% in all species. First-pass metabolism of ximelagatran with subsequent biliary excretion of the formed metabolites account for the lower bioavailability of melagatran.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 159776-70-2, Melagatran 192939-46-1, Ximelagatran 192939-72-3
303184-53-4
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(absorption, distribution, metabolism, and excretion of ximelagatran, an oral direct thrombin inhibitor, in rats, dogs, and humans)

L1 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:99008 CAPLUS
DOCUMENT NUMBER: 139:62516
TITLE: Determination of ximelagatran, an oral direct thrombin inhibitor, its active metabolite melagatran, and the intermediate metabolites, in biological samples by liquid chromatography-mass spectrometry
AUTHOR(S): Larsson, Marita; Ahnoff, Martin; Abrahamsson, Anna; Logren, Ulrika; Fakt, Christina; Ohrman, Irene; Persson, Bengt-Arne
CORPORATE SOURCE: DMPK and Bioanalytical Chemistry, AstraZeneca R and D Molndal, Moelndal, S-431 83, Swed.
SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2003), 783(2), 335-347
CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Anal. methods for the determination of ximelagatran, an oral direct thrombin inhibitor, its active metabolite melagatran, and intermediate metabolites, melagatran hydroxyamidine and melagatran Et ester, in biol. samples by liquid chromatog. (LC) pos. electrospray ionization mass spectrometry (MS) using selected reaction monitoring are described. Isolation from human plasma was achieved by solid-phase extraction on octylsilica. Analytes and isotope-labeled internal stds. were separated by LC utilizing a C18 anal. column and a mobile phase comprising acetonitrile-4 mmol/L ammonium acetate (35:65, volume/volume) containing 0.1% formic acid, at a flow-rate of 0.75 mL/min. Absolute recovery was .apprx.80% for ximelagatran, .apprx.60% for melagatran Et ester, and >90% for melagatran and melagatran hydroxyamidine. Limit of quantification was 10 nmol/L, with a relative standard deviation <20% for each analyte and <5% above 100 nmol/L. Procedures for the determination of these analytes in human urine and breast milk, plus whole

blood from rat and mouse are also described.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 159776-70-2, Melagatran 192939-46-1, Ximelagatran 192939-72-3, Melagatran hydroxyamidine **303184-53-4**, Melagatran ethyl ester
RL: ANT (Analyte); ANST (Analytical study)
(ximelagatran and its active metabolite melagatran and intermediate metabolites determination in biol. samples by liquid chromatog.-mass spectrometry)

L1 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:416776 CAPLUS
DOCUMENT NUMBER: 135:14329
TITLE: Antithrombotic pharmaceutical combinations including a P2T receptor antagonist
INVENTOR(S): Dixon, John; Humphries, Robert; Jarvis, Gavin; Kirk, Ian
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001039781	A1	20010607	WO 2000-SE2378	20001129
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2391161	AA	20010607	CA 2000-2391161	20001129
BR 2000016043	A	20020723	BR 2000-16043	20001129
EP 1237559	A1	20020911	EP 2000-982033	20001129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003515565	T2	20030507	JP 2001-541513	20001129
EE 200200271	A	20030616	EE 2002-271	20001129
NZ 518904	A	20040227	NZ 2000-518904	20001129
RU 2242232	C2	20041220	RU 2002-117296	20001129
NZ 530058	A	20050429	NZ 2000-530058	20001129
ZA 2002003707	A	20030811	ZA 2002-3707	20020509
NO 2002002606	A	20020711	NO 2002-2606	20020531
US 2003032618	A1	20030213	US 2002-148526	20020531
PRIORITY APPLN. INFO.:			SE 1999-4377 A	19991201
			WO 2000-SE2378 W	20001129

AB The invention provides pharmaceutical combinations and their use in anti-thrombotic therapy. The combinations include a P2T receptor antagonist and another antithrombotic agent.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 50-78-2, Aspirin 81-81-2, Warfarin 9005-49-6, Heparin, biological studies 55142-85-3, Ticlopidine 113665-84-2, Clopidogrel 139639-23-9, Tissue plasminogen activator 159776-70-2, Melagatran 163706-06-7 164992-25-0 191588-94-0, Tenecteplase 201304-22-5, GR144053 **303184-53-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antithrombotic pharmaceutical combinations including P2T receptor antagonist)

L1 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:772474 CAPLUS
DOCUMENT NUMBER: 133:340244
TITLE: A pharmaceutical formulation comprising a low molecular weight thrombin inhibitor and its prodrug
INVENTOR(S): Gustafsson, David
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000064470	A1	20001102	WO 2000-SE756	20000419
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
SE 9901442	A	20001022	SE 1999-1442	19990421
SE 523811	C2	20040518		
CA 2371008	AA	20001102	CA 2000-2371008	20000419
BR 2000009847	A	20020108	BR 2000-9847	20000419
EP 1200118	A1	20020502	EP 2000-928047	20000419
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
TR 200103017	T2	20020521	TR 2001-200103017	20000419
AU 754405	B2	20021114	AU 2000-46336	20000419
JP 2002542298	T2	20021210	JP 2000-613460	20000419
EE 200100543	A	20030217	EE 2001-543	20000419
NZ 514827	A	20050128	NZ 2000-514827	20000419
RU 2252783	C2	20050527	RU 2001-128157	20000419
ZA 2001008544	A	20030117	ZA 2001-8544	20011017
NO 2001005107	A	20011019	NO 2001-5107	20011019
PRIORITY APPLN. INFO.:			SE 1999-1442 A	19990421
			SE 1999-4419 A	19991203
			WO 2000-SE756 W	20000419

OTHER SOURCE(S): MARPAT 133:340244

AB A pharmaceutical formulation contains a low mol. weight thrombin inhibitor, or a pharmaceutically acceptable derivative with an adjuvant, diluent or carrier; a pharmaceutical formulation including a prodrug of a low mol. weight thrombin inhibitor, or a derivative of that prodrug, in admixt. with an adjuvant, diluent or carrier. The formulation is suitable for administration in the treatment of a condition in which the inhibition of thrombin is required. A controlled, randomized, parallel group, Swedish multi-center pilot study was carried out. The study was open with regard to the drugs under evaluation but was blind for the patients, all personnel at the study sites, and for the person monitoring the expts. with regard to the doses of melagatran and the prodrug of melagatran, EtOOC-CH2-(R)Cgl-Aze-Pab-OH (I). A combination of s.c. administered melagatran and orally administered I is effective in preventing venous thrombosis after orthopedic surgery.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 159776-70-2D, Melagatran, prodrugs **303184-53-4** 303184-54-5

303184-55-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation comprising low mol. weight thrombin inhibitor and its prodrug)

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NEWS	4	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	5	MAR 02	GBFULL: New full-text patent database on STN
NEWS	6	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	8	MAR 22	KOREAPAT now updated monthly; patent information enhanced
NEWS	9	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
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NEWS	11	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS	12	APR 04	EPFULL enhanced with additional patent information and new fields
NEWS	13	APR 04	EMBASE - Database reloaded and enhanced
NEWS	14	APR 18	New CAS Information Use Policies available online
NEWS	15	APR 25	Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAplus and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS	16	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
NEWS	17	MAY 23	GBFULL enhanced with patent drawing images
NEWS	18	MAY 23	REGISTRY has been enhanced with source information from CHEMCATS
NEWS	19	JUN 06	STN Patent Forums to be held in June 2005
NEWS	20	JUN 06	The Analysis Edition of STN Express with Discover! (Version 8.0 for Windows) now available
NEWS	21	JUN 13	RUSSIAPAT: New full-text patent database on STN

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 NEWS  22 JUN 13  FRFULL enhanced with patent drawing images
 NEWS  23 JUN 20  MEDICONF to be removed from STN

 NEWS EXPRESS  JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

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=> s 159776-70-2
L1          833 159776-70-2

=> s transfusion and l1
L2           18 TRANSFUSION AND L1

=> s transplantation and l1
L3            9 TRANSPLANTATION AND L1

=> s islet(1w)langerhan# and l1
L4            2 ISLET(1W) LANGERHAN# AND L1

=> d l1-l3 ibib abs kwic
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=> d l1 ibib abs kwic

L1 ANSWER 1 OF 833 MEDLINE on STN
ACCESSION NUMBER: 2005208363 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15842280
TITLE: The oral direct thrombin inhibitor, ximelagatran, an alternative for anticoagulant treatment during the puerperium and lactation.
AUTHOR: Hellgren M; Johansson S; Eriksson U G; Wahlander K
CORPORATE SOURCE: Department of Antenatal Care, Primary Health Care South Bohuslan and Institute for the Health of Women and Children, Sahlgrenska Hospital/East, University of Goteborg, S-416 85 Goteborg, Sweden.
SOURCE: BJOG : an international journal of obstetrics and gynaecology, (2005 May) 112 (5) 579-83.
Journal code: 100935741. ISSN: 1470-0328.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 20050422
Last Updated on STN: 20050615
Entered Medline: 20050614

AB OBJECTIVE: To determine the excretion of the oral direct thrombin inhibitor (oral DTI), ximelagatran, and its active form, melagatran, in human milk, and to thus evaluate the potential exposure of breastfed infants to melagatran. DESIGN: An open, single dose, single centre study. SETTING: Department of Antenatal Care, Primary Health Care South Bohuslan and Institute for the Health of Women and Children, Goteborg University, Sweden. SAMPLE: Seven healthy Caucasian breastfeeding women who were at least two months postpartum were studied. METHODS: The concentrations of ximelagatran, its two intermediates, and melagatran were determined using liquid chromatography-mass spectrometry, with the limit of quantification of 2 nmol L(-1) for human milk and 10 nmol L(-1) for plasma concentrations. MAIN OUTCOME MEASURES: Concentrations of ximelagatran, its intermediates and melagatran were measured in breast milk over 72 hours, and in plasma over 12 hours, after a single oral 36 mg dose of ximelagatran. RESULTS: Neither ximelagatran nor its intermediates were detected in human breast milk. Only trace amounts of melagatran were detected. The mean cumulative amount of melagatran excreted into breast milk over the 72-hour period after dosing with oral ximelagatran was 0.00091% of the administered dose of ximelagatran. Ximelagatran was well tolerated, with no clinically relevant changes in laboratory variables or vital signs. CONCLUSIONS: Trace levels of melagatran are excreted in human breast milk following administration of the oral DTI ximelagatran. The exposure of breastfed infants to melagatran appears to be low and is therefore unlikely to be of clinical concern.
RN **159776-70-2 (melagatran)**; 56-40-6 (Glycine)

=> d l2 1-18 ibib abs kwic

L2 ANSWER 1 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2004366716 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15269843
TITLE: Significantly lower need for blood transfusions associated with post-operatively initiated subcutaneous melagatran/oral ximelagatran compared with enoxaparin.
AUTHOR: Eriksson Bengt I; Agnelli Giancarlo; Cohen Alexander; Dahl Ola; Mouret Patrick; Rosencher Nadia; Panfilov Seva; Andersson Magnus
CORPORATE SOURCE: METHRO III Study Investigators.
SOURCE: Thrombosis and haemostasis, (2004 Aug) 92 (2) 428-30. Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Letter
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 20040723
Last Updated on STN: 20050216
Entered Medline: 20050215
CT Administration, Oral
*Anticoagulants: PD, pharmacology
Arthroplasty, Replacement, Hip
Arthroplasty, Replacement, Knee
*Azetidines: PD, pharmacology
***Blood Transfusion**
Drug Therapy, Combination
*Enoxaparin: PD, pharmacology
*Glycine: AA, analogs & derivatives
*Glycine: PD, pharmacology
Humans
Logistic Models
Odds Ratio
. . .
RN **159776-70-2 (melagatran)**; 56-40-6 (Glycine)

L2 ANSWER 2 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2004127988 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15018597
TITLE: Ximelagatran/Melagatran: a review of its use in the prevention of venous thromboembolism in orthopaedic surgery.
AUTHOR: Evans Hannah C; Perry Caroline M; Faulds Diana
CORPORATE SOURCE: Adis International Limited, 41 Centorian Drive, PB 65901, Mairangi Bay, Auckland 1311, New Zealand.. demail@adis.co.nz
SOURCE: Drugs, (2004) 64 (6) 649-78. Ref: 65
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 20040316
Last Updated on STN: 20040810
Entered Medline: 20040809
AB Ximelagatran (Exanta), the first available oral direct thrombin inhibitor, and its active form, melagatran, have been evaluated in the prevention of

venous thromboembolism (VTE) in patients undergoing hip or knee replacement.After oral administration ximelagatran is rapidly bioconverted to melagatran. Melagatran inactivates both circulating and clot-bound thrombin by binding to the thrombin active site, thus, inhibiting platelet activation and/or aggregation and reducing fibrinolysis time.The efficacy of subcutaneous melagatran followed by oral ximelagatran has been investigated in four European trials and the efficacy of an all oral ximelagatran regimen has been investigated in five US trials. In a dose-ranging European study, preoperatively initiated subcutaneous melagatran 3 mg twice daily followed by oral ximelagatran 24 mg twice daily was significantly more effective than subcutaneous dalteparin sodium 5000IU once daily in preventing the occurrence of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients undergoing hip or knee replacement. In one study, there were no significant differences in VTE prevention between subcutaneous melagatran 3 mg administered after surgery followed by ximelagatran 24 mg twice daily and enoxaparin sodium (enoxaparin) 40 mg once daily. Compared with enoxaparin, significantly lower rates of proximal DVT and/or PE (major VTE) and total VTE were observed when melagatran was initiated preoperatively (2mg) then postoperatively (3mg) and followed by ximelagatran 24 mg twice daily. In the US, four studies showed that postoperatively initiated ximelagatran 24 mg twice daily was of similar efficacy to enoxaparin or warfarin in the prevention of VTE in patients undergoing hip or knee replacement. However, ximelagatran 36 mg twice daily was superior to warfarin (target international normalised ratio of 2.5) at preventing the incidence of VTE in patients undergoing total knee replacement in two studies.Ximelagatran alone or after melagatran was generally well tolerated. Overall, the incidence of bleeding events and **transfusion** rates were not markedly different from those documented for comparator anticoagulants. In a post-hoc analysis of one study, **transfusion** rates were lower in ximelagatran than enoxaparin recipients.CONCLUSIONS: Oral ximelagatran alone or in conjunction with subcutaneous melagatran has shown good efficacy and was generally well tolerated in the prevention of VTE in patients undergoing orthopaedic surgery. Furthermore, patients receiving ximelagatran/melagatran do not require anticoagulant monitoring. The drug has a low potential for drug interactions and can be administered either by subcutaneous injection or orally. Thus, on the basis of available evidence, ximelagatran/melagatran appears poised to play an important role in the prophylaxis of VTE in patients undergoing orthopaedic surgery.

AB . . . knee replacement in two studies.Ximelagatran alone or after melagatran was generally well tolerated. Overall, the incidence of bleeding events and **transfusion** rates were not markedly different from those documented for comparator anticoagulants. In a post-hoc analysis of one study, **transfusion** rates were lower in ximelagatran than enoxaparin recipients.CONCLUSIONS: Oral ximelagatran alone or in conjunction with subcutaneous melagatran has shown good. . .

RN **159776-70-2 (melagatran)**; 56-40-6 (Glycine); 81-81-2 (Warfarin)

L2 ANSWER 3 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:145587 BIOSIS

DOCUMENT NUMBER: PREV200500144634

TITLE: Postoperative melagatran/ximelagatran for the prevention of venous thromboembolism following major elective orthopaedic surgery - Effects of timing of first dose and risk factors for thromboembolism and bleeding complications on efficacy and safety.

AUTHOR(S): Dahl, Ola E. [Reprint Author]; Eriksson, Bengt I.; Agnelli, Giancarlo; Cohen, Alexander T.; Mouret, Patrick; Rosencher, Nadia; Panfilov, Seva; Bylock, Anders; Andersson, Magnus

CORPORATE SOURCE: Thrombosis Res Inst, Emmanuel Kaye Bldg,Manresa Rd, London, SW3 6LR, UK
oladahl@start.no

SOURCE: Clinical Drug Investigation, (2005) Vol. 25, No. 1, pp. 65-77. print.

ISSN: 1173-2563 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Apr 2005
Last Updated on STN: 13 Apr 2005

AB Objectives: To examine the influence of timing of postoperative initiation of subcutaneous melagatran followed by oral ximelagatran, and of risk factors for venous thromboembolism (VTE; including deep vein thrombosis (DVT) and pulmonary embolism (PE)) and bleeding complications, on the efficacy and safety of this regimen, compared with preoperative enoxaparin sodium, following total hip replacement (THR) or total knee replacement (TKR) surgery. Design: Statistical analyses of efficacy and safety in subgroups of the METHRO III intention-to-treat population. Main outcome measures: Main efficacy outcome measures were major VTE (proximal DVT, PE or VTE-related death) and total VTE (distal or proximal DVT, fatal or non-fatal PE). The main safety outcome measures were blood **transfusion**, severe bleeding events, blood loss, bleeding-related adverse events and need for reoperation. Results: In the combined THR and TKR population, melagatran initiated 4 - <8 hours postoperatively was non-inferior to enoxaparin sodium with respect to the risks of total VTE (absolute risk reduction (ARR) 0; 95% confidence interval (CI) -4.4, 4.4) and major VTE (ARR -0.63; 95% CI -2.94, 1.67). The rate of major VTE was unaffected by the different risk factors. In the combined THR and TKR population, blood **transfusion** requirements were lower with melagatran/ximelagatran than enoxaparin sodium (odds ratio 0.83; 95% CI 0.71, 0.96; p = 0.016). Conclusions: Melagatran/ximelagatran initiated 4 - <8 hours postoperatively provided a comparable level of protection against total and major VTE to preoperative enoxaparin sodium. Major VTE rates and safety were consistent across different patient subgroups. Subcutaneous melagatran followed by fixed-dose oral ximelagatran offers an alternative to the standard European low molecular-weight heparin regimen in a wide range of patients.

AB. . . VTE-related death) and total VTE (distal or proximal DVT, fatal or non-fatal PE). The main safety outcome measures were blood **transfusion**, severe bleeding events, blood loss, bleeding-related adverse events and need for reoperation. Results: In the combined THR and TKR population,. . . The rate of major VTE was unaffected by the different risk factors. In the combined THR and TKR population, blood **transfusion** requirements were lower with melagatran/ximelagatran than enoxaparin sodium (odds ratio 0.83; 95% CI 0.71, 0.96; p = 0.016). Conclusions: Melagatran/ximelagatran. . .

IT Methods & Equipment
blood **transfusion**: clinical techniques, therapeutic and prophylactic techniques; major elective orthopedic surgery: clinical techniques, therapeutic and prophylactic techniques; total hip replacement: clinical. . .

RN 9005-49-6 (enoxaparin)
159776-70-2 (melagatran)
192939-46-1 (ximelagatran)

L2 ANSWER 4 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:83229 BIOSIS
DOCUMENT NUMBER: PREV200500083419
TITLE: Hemostatic agents.
AUTHOR(S): Levy, Jerrold H. [Reprint Author]
CORPORATE SOURCE: Dept Anesthesiol, Emory Univ Hosp, 1364 Clifton Rd NE, Atlanta, GA, 30322, USA
Jerrold_levy@emoryhealthcare.org
SOURCE: Transfusion (Malden), (December 2004) Vol. 44, No. 12, Suppl. S, pp. 58S-62S. print.
ISSN: 0041-1132 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Feb 2005
Last Updated on STN: 23 Feb 2005

IT Methods & Equipment
transfusion: clinical techniques, therapeutic and prophylactic techniques
RN 9087-70-1 (aprotinin)
113665-84-2 (clopidogrel)
60-32-2 (epsilon-aminocaproic acid)
104993-28-4 (fondaparinux)
159776-70-2 (melagatran)
9002-04-4 (thrombin)
9002-04-4 (EC 3.4.21.5)
1197-18-8 (tranexamic acid)

L2 ANSWER 5 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:429580 BIOSIS
DOCUMENT NUMBER: PREV200400433293
TITLE: Significantly lower need for blood transfusions associated with posttaneous initiated subcutaneous melagatran/oral ximelagatran compared with enoxaparin.
AUTHOR(S): Eriksson, Bengt I. [Reprint Author]; Agnelli, Giancarlo; Cohen, Alexander; Dahl, Ola; Mouret, Patrick; Rosencher, Nadia; Panfilov, Seva; Andersson, Magnus; METHRO III Study Investigators
CORPORATE SOURCE: Dept Orthopaed, Sahlgrens Univ Hosp, Gothenburg, Sweden
b.eriksson@orthop.gu.se
SOURCE: Thrombosis and Haemostasis, (August 2004) Vol. 92, No. 2, pp. 428-430. print.
CODEN: THHADQ. ISSN: 0340-6245.
DOCUMENT TYPE: Letter
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Nov 2004
Last Updated on STN: 10 Nov 2004
IT Methods & Equipment
blood **transfusion**: clinical techniques, therapeutic and prophylactic techniques; orthopedic surgery: clinical techniques, therapeutic and prophylactic techniques; total hip replacement: clinical techniques, therapeutic. . .
RN 9005-49-6 (enoxaparin)
159776-70-2 (melagatran)
9002-04-4 (thrombin)
9002-04-4 (EC 3.4.21.5)
192939-46-1 (ximelagatran)

L2 ANSWER 6 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:263854 BIOSIS
DOCUMENT NUMBER: PREV200400263553
TITLE: Pharmacokinetics, preliminary efficacy and safety of subcutaneous melagatran and oral Ximelagatran - A multicentre study of thromboprophylaxis in elective abdominal surgery.
AUTHOR(S): Bergqvist, David [Reprint Author]; Solhaug, Jan-Helge; Holmdahl, Lena; Erikssan, Ulf G.; Andersson, Magnus; Boberg, Barbro; Ogren, Mats
CORPORATE SOURCE: Dept Surg, Univ Uppsala Hosp, S-75185, Uppsala, Sweden
David.Bergqvist@kirurgi.uu-se
SOURCE: Clinical Drug Investigation, (2004) Vol. 24, No. 3, pp. 127-136. print.
ISSN: 1173-2563 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 19 May 2004
Last Updated on STN: 19 May 2004
AB Objective: The oral direct thrombin inhibitor (oral DTI) ximelagatran and its active form, melagatran, which can be administered subcutaneously, were investigated for the prevention and treatment of thromboembolic complications. Design and patients: In this randoinised, double-blind,

double-dummy, parallel-group study in patients (n = 90) undergoing general abdominal and/or pelvic, surgery, 8-day and 35-day treatment regimens of postoperatively initiated sub-cutaneous (sc) melagatran (3mg twice daily) followed by oral ximelagatran (24mg twice daily) were compared with standard-duration sc dalteparin (5000IU) initiated preoperatively. Pharmacodynamic and pharmacokinetic parameters, efficacy (number of patients with distal and/or proximal deep vein thrombosis, (DVT). verified by bilateral venography on the final day of treatment), and safety Were assessed. Results: The pharmacokinetics of melagatran were well described by a ones compartment model with first-order absorption after administration of both sc melagatran and oral ximelagatran. Bioavailability of melagatran was 21% after the first oral dose of ximelagatran and was virtually unchanged throughout the study. Activated partial thromboplastin time increased in a non-linear manner with plasma melagatran concentration. The overall rate of DVT was 11.4% (8/70), with events distributed evenly between treatment groups. Bleeding Volumes during surgery tended to be higher in the dalteparin group than in the melagatran/ ximelagatran groups. Blood **transfusion** volumes and numbers of patients transfused Were similar in all treatment groups. Conclusions: Good bioavailability of melagatran was achieved following oral administration of ximelagatran. Postoperative sc melagatran followed by oral-ximelagatran appeared to be well toterated, and the efficacy of standard-length or prolonged prophylaxis with sc melagatran and oral ximelagatran may be comparable to that of dalteparin initiated preoperatively.

AB. . . groups. Bleeding Volumes during surgery tended to be higher in the dalteparin group than in the melagatran/ ximelagatran groups. Blood **transfusion** volumes and numbers of patients transfused Were similar in all treatment groups. Conclusions: Good bioavailability of melagatran was achieved following. . .

IT Methods & Equipment
activated partial thromboplastin time: clinical techniques; bilateral venography: clinical techniques, diagnostic techniques; blood **transfusion**: clinical techniques, therapeutic and prophylactic techniques; elective abdominal surgery: clinical techniques, therapeutic and prophylactic techniques; one-compartment model: mathematical and computer. . .

RN 9005-49-6 (dalteparin)
159776-70-2 (melagatran)
192939-46-1 (ximelagatran)

L2 ANSWER 7 OF 18 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:356337 BIOSIS
DOCUMENT NUMBER: PREV200300356337
TITLE: The Oral Direct Thrombin Inhibitor Ximelagatran, and Its Subcutaneous (sc) Form Melagatran, Compared with Enoxaparin for Prophylaxis of Venous Thromboembolism (VTE) in Total Hip or Total Knee Replacement (THR or TKR): The EXPRESS Study.
AUTHOR(S): Eriksson, Bengt I. [Reprint Author]; Agnelli, Giancarlo [Reprint Author]; Cohen, Alexander T. [Reprint Author]; Dahl, Ola E. [Reprint Author]; Lassen, Michael R. [Reprint Author]; Mouret, Patrick [Reprint Author]; Rosencher, Nadia [Reprint Author]; Kalebo, Peter [Reprint Author]; Panfilov, Seva [Reprint Author]; Eskilson, Christina [Reprint Author]; Nylander, Ingela [Reprint Author]; Andersson, Magnus [Reprint Author]
CORPORATE SOURCE: on Behalf of the Study Investigators Department of Orthopedics and Department of Radiology, Sahlgrenska University Hospital/ostra, Goteborg, Sweden
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 299. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003

AB Introduction: Ximelagatran is a novel, oral direct thrombin inhibitor under development for the prophylaxis and treatment of thromboembolic disease. Pre- and postoperative regimens of ximelagatran, and its sc form, melagatran, have previously been evaluated in THR and TKR. This study aimed to investigate the efficacy and safety of a new dosage regimen of this thrombin inhibitor started in close proximity to surgery. Methods: In this randomized, double-blind, parallel-group study, one group of patients received sc melagatran 2 mg immediately before surgery followed by sc 3 mg in the evening after surgery, and then by oral ximelagatran 24 mg bid as a fixed dose (the ximelagatran group). The other group received sc enoxaparin 40 mg od, started the evening before surgery. Total duration of active treatments was 8 to 11 days. Bilateral venography was performed on the final day of treatment. Results: Of the 2764 patients in the ITT population (n = 1856 (THR) and n = 908 (TKR)), 82% had an evaluable venogram. The majority of patients (92%) started oral therapy the morning after surgery. The rate of proximal deep vein thrombosis plus pulmonary embolism (the study's primary endpoint) was 2.3% in the ximelagatran group and 6.3% in the enoxaparin group ($P < 0.000002$; RRR 63.2%). The total rate of VTE was 20.3% in the ximelagatran group and 26.6% in the enoxaparin group ($P < 0.0003$; RRR 23.6%). Cases with symptomatic VTE were rare: 8 in the ximelagatran group and 12 in the enoxaparin group. Bleeding events were more common in the ximelagatran group compared with the enoxaparin group (3.3% vs 1.2%), as were the **transfusion** rates (66.8% vs 61.7%). There were no differences in clinically important bleeding events (fatal bleeding, critical organ bleeding, or bleeding requiring reoperation). Conclusion: Preoperatively initiated sc melagatran followed by oral ximelagatran was superior in efficacy to enoxaparin in preventing VTE in patients undergoing THR or TKR.

AB. . . Bleeding events were more common in the ximelagatran group compared with the enoxaparin group (3.3% vs 1.2%), as were the **transfusion** rates (66.8% vs 61.7%). There were no differences in clinically important bleeding events (fatal bleeding, critical organ bleeding, or bleeding. . .

RN 9005-49-6 (enoxaparin)
159776-70-2 (melagatran)
192939-46-1 (ximelagatran)

L2 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:683877 CAPLUS
DOCUMENT NUMBER: 142:211894
TITLE: Significantly lower need for blood transfusions associated with postoperatively initiated subcutaneous melagatran/oral ximelagatran compared with enoxaparin. Comments
AUTHOR(S): Eriksson, Bengt I.; Agnelli, Giancarlo; Cohen, Alexander; Dahl, Ola; Mouret, Patrick; Rosencher, Nadia; Panfilov, Seva; Andersson, Magnus
CORPORATE SOURCE: METHRO III Study Investigators, Department of Orthopaedics, Sahlgrenska University Hospital/Oestra, Goeteborg, Swed.
SOURCE: Thrombosis and Haemostasis (2004), 92(2), 428-430
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In a randomized, double-blind study of 2788 patients undergoing total hip replacement (THR) or total knee replacement (TKR), the efficacy and safety

of the novel, oral direct thrombin inhibitor ximelagatran and its active form melagatran were previously evaluated in comparison with the low-mol.-weight heparin enoxaparin for the prevention of venous thromboembolic events after major elective orthopedic surgery. A postoperatively initiated regimen (4-12 h after surgery) of s.c. melagatran 3 mg followed by oral ximelagatran 24 mg twice daily was comparable to preoperatively initiated (12 h before surgery) enoxaparin 40 mg once daily, in terms of efficacy and the incidence of severe bleeding. A further anal. of the **transfusion** rates within each treatment group was made. Between-treatment comparisons revealed that the postoperative s.c. melagatran/oral ximelagatran regimen is associated with a significantly lower need for blood transfusions than the enoxaparin regimen. In addition, the need for blood transfusions in patients receiving melagatran/ximelagatran was independent of the timing of the initiation of the prophylaxis (< 8 h vs. ≥ 8 h after surgery). Overall, the postoperative s.c. melagatran/oral ximelagatran regimen was associated with a numerically lower median **transfusion** volume than enoxaparin.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB In a randomized, double-blind study of 2788 patients undergoing total hip replacement (THR) or total knee replacement (TKR), the efficacy and safety of the novel, oral direct thrombin inhibitor ximelagatran and its active form melagatran were previously evaluated in comparison with the low-mol.-weight heparin enoxaparin for the prevention of venous thromboembolic events after major elective orthopedic surgery. A postoperatively initiated regimen (4-12 h after surgery) of s.c. melagatran 3 mg followed by oral ximelagatran 24 mg twice daily was comparable to preoperatively initiated (12 h before surgery) enoxaparin 40 mg once daily, in terms of efficacy and the incidence of severe bleeding. A further anal. of the **transfusion** rates within each treatment group was made. Between-treatment comparisons revealed that the postoperative s.c. melagatran/oral ximelagatran regimen is associated with a significantly lower need for blood transfusions than the enoxaparin regimen. In addition, the need for blood transfusions in patients receiving melagatran/ximelagatran was independent of the timing of the initiation of the prophylaxis (< 8 h vs. ≥ 8 h after surgery). Overall, the postoperative s.c. melagatran/oral ximelagatran regimen was associated with a numerically lower median **transfusion** volume than enoxaparin.

ST blood **transfusion** melagatran ximelagatran enoxaparin thromboembolism antithrombotic hemorrhage

IT Anticoagulants
Blood **transfusion**
Hemorrhage
Human
(blood transfusions needs reduced with postoperatively initiated s.c. melagatran/oral ximelagatran vs. enoxaparin.)

IT **159776-70-2**, Melagatran 192939-46-1, Ximelagatran 679809-58-6, Enoxaparin sodium
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood transfusions needs reduced with postoperatively initiated s.c. melagatran/oral ximelagatran vs. enoxaparin.)

L2 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:367852 CAPLUS

DOCUMENT NUMBER: 141:847

TITLE: Pharmacokinetics, preliminary efficacy and safety of subcutaneous melagatran and oral ximelagatran: A multicentre study of thromboprophylaxis in elective abdominal surgery

AUTHOR(S): Bergqvist, David; Solhaug, Jan-Helge; Holmdahl, Lena; Eriksson, Ulf G.; Andersson, Magnus; Boberg, Barbro; Ogren, Mats

CORPORATE SOURCE: Uppsala University Hospital, Uppsala, Swed.

SOURCE: Clinical Drug Investigation (2004), 24(3), 127-136

CODEN: CDINFR; ISSN: 1173-2563
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The oral direct thrombin inhibitor (oral DTI) ximelagatran and its active form, melagatran, which can be administered s.c., were investigated for the prevention and treatment of thromboembolic complications. Design and patients: In this randomized, double-blind, double-dummy, parallel-group study in patients (n = 90) undergoing general abdominal and/or pelvic surgery, 8-day and 35-day treatment regimens of postoperatively initiated s.c. (s.c.) melagatran (3mg twice daily) followed by oral ximelagatran (24mg twice daily) were compared with standard-duration s.c. dalteparin (5000IU) initiated preoperatively. Pharmacodynamic and pharmacokinetic parameters, efficacy (number of patients with distal and/or proximal deep vein thrombosis [DVT] verified by bilateral venog. on the final day of treatment) and safety were assessed. Results: The pharmacokinetics of melagatran were well described by a one-compartment model with first-order absorption after administration of both s.c. melagatran and oral ximelagatran. Bioavailability of melagatran was 21% after the first oral dose of ximelagatran and was virtually unchanged throughout the study. Activated partial thromboplastin time increased in a non-linear manner with plasma melagatran concentration The overall rate of DVT was 11.4% (8/70), with events distributed evenly between treatment groups. Bleeding vols. during surgery tended to be higher in the dalteparin group than in the melagatran/ximelagatran groups. Blood **transfusion** vols. and nos. of patients transfused were similar in all treatment groups. Conclusions: Good bioavailability of melagatran was achieved following oral administration of ximelagatran. Postoperative s.c. melagatran followed by oral ximelagatran appeared to be well tolerated, and the efficacy of standard-length or prolonged prophylaxis with s.c. melagatran and oral ximelagatran may be comparable to that of dalteparin initiated preoperatively.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB The oral direct thrombin inhibitor (oral DTI) ximelagatran and its active form, melagatran, which can be administered s.c., were investigated for the prevention and treatment of thromboembolic complications. Design and patients: In this randomized, double-blind, double-dummy, parallel-group study in patients (n = 90) undergoing general abdominal and/or pelvic surgery, 8-day and 35-day treatment regimens of postoperatively initiated s.c. (s.c.) melagatran (3mg twice daily) followed by oral ximelagatran (24mg twice daily) were compared with standard-duration s.c. dalteparin (5000IU) initiated preoperatively. Pharmacodynamic and pharmacokinetic parameters, efficacy (number of patients with distal and/or proximal deep vein thrombosis [DVT] verified by bilateral venog. on the final day of treatment) and safety were assessed. Results: The pharmacokinetics of melagatran were well described by a one-compartment model with first-order absorption after administration of both s.c. melagatran and oral ximelagatran. Bioavailability of melagatran was 21% after the first oral dose of ximelagatran and was virtually unchanged throughout the study. Activated partial thromboplastin time increased in a non-linear manner with plasma melagatran concentration The overall rate of DVT was 11.4% (8/70), with events distributed evenly between treatment groups. Bleeding vols. during surgery tended to be higher in the dalteparin group than in the melagatran/ximelagatran groups. Blood **transfusion** vols. and nos. of patients transfused were similar in all treatment groups. Conclusions: Good bioavailability of melagatran was achieved following oral administration of ximelagatran. Postoperative s.c. melagatran followed by oral ximelagatran appeared to be well tolerated, and the efficacy of standard-length or prolonged prophylaxis with s.c. melagatran and oral ximelagatran may be comparable to that of dalteparin initiated preoperatively.
IT **159776-70-2**, Melagatran 192939-46-1, Exanta
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological

study); USES (Uses)
(pharmacokinetics, efficacy and safety of s.c. melagatran and oral ximelagatran for thromboprophylaxis following abdominal surgery)

L2 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:150481 CAPLUS
DOCUMENT NUMBER: 136:319112
TITLE: A dose-ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prophylaxis of thromboembolism after hip or knee replacement: METHRO I
AUTHOR(S): Eriksson, Bengt I.; Arfwidsson, Ann-Christin; Frison, Lars; Eriksson, Ulf G.; Bylock, Anders; Kalebo, Peter; Fager, Gunnar; Gustafsson, David
CORPORATE SOURCE: Department of Orthopaedic Surgery, Sahlgrenska University Hospital/Ostra, Goteborg, S-41685, Swed.
SOURCE: Thrombosis and Haemostasis (2002), 87(2), 231-237
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The novel, oral direct thrombin inhibitor, ximelagatran (formerly H 376/95), represents an advance in antithrombotic therapy through its oral availability. After oral administration, ximelagatran is converted to its active form, melagatran. Melagatran can also be administered s.c. (s.c.). The results from the first clin. study with ximelagatran are reported. In this randomized, parallel-group, controlled study, 103 patients scheduled for elective total hip or total knee replacement received s.c. melagatran (1, 2 or 4 mg bid) for 2 days commencing immediately before surgery, followed by oral ximelagatran (6, 12 or 24 mg bid) for 6-9 days. Another 33 patients received dalteparin 5000 IU s.c. once daily, started the evening before surgery, for 8-11 days. At bilateral venog., deep vein thrombosis was found in 20.5% (16/78) of patients who had received s.c. melagatran and oral ximelagatran and in 18.5% (5/27) of patients in the dalteparin group. The study did not evaluate a dose-response for efficacy, and no differences between the three dose levels of melagatran and ximelagatran were shown. No pulmonary embolism was diagnosed during treatment. Total bleeding in the s.c. melagatran plus oral ximelagatran groups showed no dose-response and was similar to that seen in the dalteparin group. The pharmacokinetic properties of melagatran in the surgery patients were consistent with those observed for healthy subjects, and the APTT ratio, which increased non-linearly with plasma melagatran concentration, showed a consistent concentration-effect relationship during the treatment period. Ximelagatran and melagatran were well tolerated. In conclusion, ximelagatran and its active form melagatran appear to be promising agents for the prevention of venous thromboembolism following orthopedic surgery.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
ST anticoagulant ximelagatran melagatran dalteparin thromboembolism prevention orthopedic surgery; ximelagatran melagatran bleeding blood **transfusion** thrombosis hip knee replacement; melagatran pharmacokinetics bioavailability
IT Anticoagulants
Blood **transfusion**
Drug bioavailability
Human
(oral direct thrombin inhibitor, ximelagatran, and s.c. form, melagatran, compared with dalteparin for prevention of thromboembolism in hip or knee replacement patients)
IT **159776-70-2**, Melagatran 192939-46-1, Ximelagatran
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(oral direct thrombin inhibitor, ximelagatran, and s.c. form, melagatran, compared with dalteparin for prevention of thromboembolism in hip or knee replacement patients)

L2 ANSWER 11 OF 18 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2005037751 EMBASE
TITLE: Recombinant activated factor VII in patients at high risk of bleeding.
AUTHOR: Kubisz P.; Stasko J.
CORPORATE SOURCE: P. Kubisz, Dept. of Hematol./Blood Transfusion, Jessenius Medical-School, Comenius University, Kollarova 2, 036 59 Martin, Slovakia. kubisz@jfmed.uniba.sk
SOURCE: Hematology, (2004) Vol. 9, No. 5-6, pp. 317-332.
Refs: 111
ISSN: 1024-5340 CODEN: HMATFL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050204
Last Updated on STN: 20050204

AB Currently, recombinant activated factor VII (rFVIIa) (NovoSeven®) is indicated for the treatment of spontaneous and surgical bleeding in congenital haemophilia A and B patients with inhibitors to factors VIII (FVIII) and IX (FIX) > 5 Bethesda units (BU) worldwide, and in patients with acquired haemophilia, congenital FVII deficiency and Glanzmann's thrombasthenia in Europe. Until April 2003, almost three-quarters of a milion doses of rFVIIa have been administered proving its efficacy and excellent safety record. According to results from initial clinical trials and a large number of case reports, the rFVIIa may be effective not only in treating haemophilia patients but also in treatment of bleeding in patients on oral anticoagulation or heparin, patients with liver diseases, von Willebrand disease (vWD), thrombocytopenia, various platelet defects, congenital or acquired deficiency of FVII, and in subjects without any pre-existing coagulopathy with diffuse life-threatening bleeding triggered by surgery or trauma. This review will briefly summarize rFVIIa mode of action in haemostasis, the current clinical experience with rFVIIa and focus on the alternative use of rFVIIa in patients at the high risk of bleeding in both spontaneous cases and clinical trials reports. .COPYRGT. 2004 Taylor & Francis Ltd.

CT Medical Descriptors:
*bleeding . . . therapy
thrombocytopenia: PC, prevention
thrombocyte anomaly: DT, drug therapy
drug mechanism
drug half life
hospital admission
thrombosis: CO, complication
thrombosis: DT, drug therapy
thrombosis: PC, prevention
thrombosis: SI, side effect
blood transfusion reaction: SI, side effect
thromboembolism: CO, complication
thromboembolism: DT, drug therapy
thromboembolism: PC, prevention
thromboembolism: SI, side effect
thrombocyte transfusion
deep vein thrombosis: CO, complication
deep vein thrombosis: DT, drug therapy

deep vein thrombosis: PC, prevention
brain hemorrhage: DT, drug therapy
brain hemorrhage: PC,. . .
RN. . . (thromboplastin) 9035-58-9; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (blood clotting factor 10) 9001-29-0; (acenocoumarol) 152-72-7; (enoxaparin) 9041-08-1; (hirudin) 8001-27-2; (melagatran) **159776-70-2**; (ximelagatran) 192939-46-1, 260790-58-7; (fondaparinux) 104993-28-4, 114870-03-0; (idraparinux) 149920-56-9, 162610-17-5; (blood clotting factor 5) 9001-24-5, 9013-23-4; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4,. . .

L2 ANSWER 12 OF 18 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2005021639 EMBASE
TITLE: Postoperative melagatran/ximelagatran for the prevention of venous thromboembolism following major elective orthopaedic surgery: Effects of timing of first dose and risk factors for thromboembolism and bleeding complications on efficacy and safety.
AUTHOR: Dahl O.E.; Eriksson B.I.; Agnelli G.; Cohen A.T.; Mouret P.; Rosencher N.; Panfilov S.; Bylock A.; Andersson M.
CORPORATE SOURCE: Dr. O.E. Dahl, Thrombosis Research Institute, Emmanuel Kaye Building, Manresa Road, London SW3 6LR, United Kingdom. oladahl@start.no
SOURCE: Clinical Drug Investigation, (2005) Vol. 25, No. 1, pp. 65-77.
Refs: 27
ISSN: 1173-2563 CODEN: CDINFR
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050127
Last Updated on STN: 20050127

AB Objectives: To examine the influence of timing of postoperative initiation of subcutaneous melagatran followed by oral ximelagatran, and of risk factors for venous thromboembolism (VTE; including deep vein thrombosis [DVT] and pulmonary embolism [PE]) and bleeding complications, on the efficacy and safety of this regimen, compared with preoperative enoxaparin sodium, following total hip replacement (THR) or total knee replacement (TKR) surgery. Design: Statistical analyses of efficacy and safety in subgroups of the METHRO III intention-to-treat population. Main outcome measures: Main efficacy outcome measures were major VTE (proximal DVT, PE or VTE-related death) and total VTE (distal or proximal DVT, fatal or non-fatal PE). The main safety outcome measures were blood **transfusion**, severe bleeding events, blood loss, bleeding-related adverse events and need for reoperation. Results: In the combined THR and TKR population, melagatran initiated 4 - <8 hours postoperatively was non-inferior to enoxaparin sodium with respect to the risks of total VTE (absolute risk reduction [ARR] 0; 95% confidence interval [CI] -4.4, 4.4) and major VTE (ARR -0.63; 95% CI -2.94, 1.67). The rate of major VTE was unaffected by the different risk factors. In the combined THR and TKR population, blood **transfusion** requirements were lower with melagatran/ ximelagatran than enoxaparin sodium (odds ratio 0.83; 95% CI 0.71, 0.96; p = 0.016). Conclusions: Melagatran/ximelagatran initiated 4 - <8 hours postoperatively provided a comparable level of protection against total and major VTE to preoperative enoxaparin sodium. Major VTE rates and safety were consistent across different patient subgroups. Subcutaneous melagatran followed by fixed-dose oral ximelagatran offers an alternative to the standard European low molecular-weight heparin regimen in a wide range of patients.

AB . . . VTE-related death) and total VTE (distal or proximal DVT, fatal or non-fatal PE). The main safety outcome measures were blood **transfusion**, severe bleeding events, blood loss, bleeding-related adverse events and need for reoperation. Results: In the combined THR and TKR population,. . . The rate of major VTE was unaffected by the different risk factors. In the combined THR and TKR population, blood **transfusion** requirements were lower with melagatran/ ximelagatran than enoxaparin sodium (odds ratio 0.83; 95% CI 0.71, 0.96; p = 0.016). Conclusions:. . .

CT Medical Descriptors:
*venous . . . surgery
*orthopedic surgery
*bleeding: SI, side effect
postoperative period
dose time effect relation
risk factor
drug safety
deep vein thrombosis
lung embolism
drug efficacy
preoperative treatment
total hip prosthesis
total knee replacement
treatment outcome
blood transfusion
disease severity
reoperation
Europe
brain hemorrhage: SI, side effect
intraocular hemorrhage: SI, side effect
spinal cord hemorrhage: SI, side effect
retroperitoneal hemorrhage: SI, side effect
human
male
female
major clinical. . .

RN (ximelagatran) 192939-46-1, 260790-58-7; (melagatran) **159776-70-2** ; (enoxaparin) 9041-08-1

L2 ANSWER 13 OF 18 EMBASE
on STN

ACCESSION NUMBER: 2004378680 EMBASE
TITLE: Significantly lower need for blood transfusions associated with post-operatively initiated subcutaneous melagatran/oral ximelagatran compared with enoxaparin [3].
AUTHOR: Eriksson B.I.; Agnelli G.; Cohen A.; Dahl O.; Mouret P.; Rosencher N.; Panfilov S.; Andersson M.
CORPORATE SOURCE: Dr. B.I. Eriksson, S-41685 Goteborg, Sweden. b.eriksson@orthop.gu.se
SOURCE: Thrombosis and Haemostasis, (2004) Vol. 92, No. 2, pp. 428-430.
Refs: 3
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 025 Hematology
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20040924
Last Updated on STN: 20040924
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

CT Medical Descriptors:
*thromboembolism: CO, complication

*thromboembolism: DT, drug therapy
*thromboembolism: PC, prevention
*thromboembolism: TH, therapy
***blood transfusion**
*anticoagulant therapy
drug safety
drug efficacy
total hip prosthesis
total knee replacement
logistic regression analysis
treatment outcome
statistical analysis
time
blood volume
bleeding: SI, side effect
human
letter
priority journal
*enoxaparin: CB, drug. . .

RN (enoxaparin) 9041-08-1; (melagatran) **159776-70-2**; (ximelagatran) 192939-46-1, 260790-58-7

L2 ANSWER 14 OF 18 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004169463 EMBASE
TITLE: Ximelagatran/melagatran: A review of its use in the prevention of venous thromboembolism in orthopaedic surgery.
AUTHOR: Evans H.C.; Perry C.M.; Faulds D.
CORPORATE SOURCE: H.C. Evans, Adis International Limited, 41 Centorian Drive, Mairangi Bay, Auckland 1311, New Zealand. demail@adis.co.nz
SOURCE: Drugs, (2004) Vol. 64, No. 6, pp. 649-678.
Refs: 65
ISSN: 0012-6667 CODEN: DRUGAY
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
033 Orthopedic Surgery
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040506
Last Updated on STN: 20040506

AB Ximelagatran (Exanta®), the first available oral direct thrombin inhibitor, and its active form, melagatran, have been evaluated in the prevention of venous thromboembolism (VTE) in patients undergoing hip or knee replacement. After oral administration ximelagatran is rapidly bioconverted to melagatran. Melagatran inactivates both circulating and clot-bound thrombin by binding to the thrombin active site, thus, inhibiting platelet activation and/or aggregation and reducing fibrinolysis time. The efficacy of subcutaneous melagatran followed by oral ximelagatran has been investigated in four European trials and the efficacy of an all oral ximelagatran regimen has been investigated in five US trials. In a dose-ranging European study, preoperatively initiated subcutaneous melagatran 3mg twice daily followed by oral ximelagatran 24mg twice daily was significantly more effective than subcutaneous dalteparin sodium 5000IU once daily in preventing the occurrence of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients undergoing hip or knee replacement. In one study, there were no significant differences in VTE prevention between subcutaneous melagatran 3mg administered after surgery followed by ximelagatran 24mg twice daily and enoxaparin sodium (enoxaparin) 40mg once daily. Compared with enoxaparin, significantly lower rates of proximal DVT and/or PE (major

VTE) and total VTE were observed when melagatran was initiated preoperatively (2mg) then postoperatively (3mg) and followed by ximelagatran 24mg twice daily. In the US, four studies showed that postoperatively initiated ximelagatran 24mg twice daily was of similar efficacy to enoxaparin or warfarin in the prevention of VTE in patients undergoing hip or knee replacement. However, ximelagatran 36mg twice daily was superior to warfarin (target international normalised ratio of 2.5) at preventing the incidence of VTE in patients undergoing total knee replacement in two studies. Ximelagatran alone or after melagatran was generally well tolerated. Overall, the incidence of bleeding events and **transfusion** rates were not markedly different from those documented for comparator anticoagulants. In a post-hoc analysis of one study, **transfusion** rates were lower in ximelagatran than enoxaparin recipients. Conclusions: Oral ximelagatran alone or in conjunction with subcutaneous melagatran has shown good efficacy and was generally well tolerated in the prevention of VTE in patients undergoing orthopaedic surgery. Furthermore, patients receiving ximelagatran/melagatran do not require anticoagulant monitoring. The drug has a low potential for drug interactions and can be administered either by subcutaneous injection or orally. Thus, on the basis of available evidence, ximelagatran/melagatran appears poised to play an important role in the prophylaxis of VTE in patients undergoing orthopaedic surgery.

AB . . . replacement in two studies. Ximelagatran alone or after melagatran was generally well tolerated. Overall, the incidence of bleeding events and **transfusion** rates were not markedly different from those documented for comparator anticoagulants. In a post-hoc analysis of one study, **transfusion** rates were lower in ximelagatran than enoxaparin recipients. Conclusions: Oral ximelagatran alone or in conjunction with subcutaneous melagatran has shown. . .

CT Medical Descriptors:
*venous . . . prevention
*orthopedic surgery
thrombocyte activation
thrombocyte aggregation
fibrinolysis
drug efficacy
drug tolerability
side effect: SI, side effect
bleeding: SI, side effect
drug bioavailability
kidney clearance
drug half life
drug elimination
drug urine level
liver failure
obesity
blood transfusion
hematoma: SI, side effect
fever: SI, side effect
nausea: SI, side effect
constipation: SI, side effect
urinary tract infection: SI, side effect
postoperative complication: CO,. . .

RN (ximelagatran) 192939-46-1, 260790-58-7; (melagatran) **159776-70-2** ; (thrombin) 9002-04-4; (enoxaparin) 9041-08-1; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (cytochrome P450) 9035-51-2; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1;. . .

L2 ANSWER 15 OF 18 EMBASE
on STN
ACCESSION NUMBER: 2003082427 EMBASE
TITLE: Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee

replacement: The METHRO III study.
AUTHOR: Eriksson B.I.; Agnelli G.; Cohen A.T.; Dahl O.E.; Mouret P.; Rosencher N.; Eskilson C.; Nylander I.; Frison L.; Ogren M.
CORPORATE SOURCE: Dr. B.I. Eriksson, Orthopaedics Department, Sahlgrenska University Hospital, OSTRA, S-41685 Goteborg, Sweden. b.eriksson@orthop.gu.se
SOURCE: Thrombosis and Haemostasis, (1 Feb 2003) Vol. 89, No. 2, pp. 288-296.
Refs: 25
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
033 Orthopedic Surgery
038 Adverse Reactions Titles
030 Pharmacology
031 Arthritis and Rheumatism
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030306
Last Updated on STN: 20030306

AB We evaluated whether a postoperative regimen with melagatran followed by oral ximelagatran, two new direct thrombin inhibitors, was an optimal regimen for thrombophylaxis in major orthopaedic surgery. In a double-blind study, 2788 patients undergoing total hip or knee replacement were randomly assigned to receive for 8 to 11 days either 3 mg of subcutaneous melagatran started 4-12 h postoperatively, followed by 24 mg of oral ximelagatran twice-daily or 40 mg of subcutaneous enoxaparin once-daily, started 12 h preoperatively. Ximelagatran was to be initiated with the first two postoperative days. The primary efficacy endpoint was venous thromboembolism (deep-vein thrombosis detected by mandatory venography, pulmonary embolism or unexplaiend death). The main safety endpoint was bleeding. Venous thromoembolism occurred in 355/1146 (31.0%) and 306/1122 (27.3%) patterns in the ximelagatran and enoxaparin group, respectively, a difference in risk of 3.7% in favour of enoxaparin (p = 0.053). Bleeding, was comparable between the two groups.

CT Medical Descriptors:
*thromboembolism: . . . obstruction: SI, side effect
necrotizing enterocolitis: SI, side effect
cardiogenic shock: SI, side effect
septicemia: SI, side effect
preoperative treatment
outcomes research
death
parallel design
drug tolerability
compression therapy
disease severity
blood transfusion
article
priority journal
*melagatran: CM, drug comparison
*melagatran: DT, drug therapy
*melagatran: CB, drug combination
*melagatran: SC, subcutaneous drug administration
*melagatran: PD, pharmacology
*melagatran: CT, clinical. . .

RN (melagatran) **159776-70-2**; (ximelagatran) 192939-46-1, 260790-58-7; (enoxaparin) 9041-08-1; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1

L2 ANSWER 16 OF 18 EMBASE
on STN

ACCESSION NUMBER: 2002413049 EMBASE
TITLE: Thrombin inhibitor more effective than enoxaparin at preventing blood clots.
SOURCE: Pharmaceutical Journal, (2 Nov 2002) Vol. 269, No. 7222, pp. 636.
ISSN: 0031-6873 CODEN: PHJOAV
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 006 Internal Medicine
015 Chest Diseases, Thoracic Surgery and Tuberculosis
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20021202
Last Updated on STN: 20021202
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER
CT Medical Descriptors:
*lung . . . therapy
*deep vein thrombosis: PC, prevention
thromboembolism: CO, complication
thromboembolism: DT, drug therapy
thromboembolism: PC, prevention
total hip prosthesis
total knee replacement
elective surgery
surgical mortality
bleeding: SI, side effect
blood transfusion
licence
United Kingdom
human
controlled study
note
*thrombin inhibitor: AE, adverse drug reaction
*thrombin inhibitor: CM, drug comparison
*thrombin inhibitor: DV, drug development
*thrombin inhibitor: DT, drug. . .
RN (enoxaparin) 9041-08-1; (melagatran) **159776-70-2**; (ximelagatran) 192939-46-1, 260790-58-7

L2 ANSWER 17 OF 18 EMBASE
on STN
ACCESSION NUMBER: 2002318033 EMBASE
TITLE: [The oral direct thrombin inhibitor ximelagatran prophylaxis of venous thromboembolism in hip and knee replacement].
DER ORALE DIREKTE THROMBININHIBITOR XIMELAGATRAN THROMBOEMBOLIEPROPHYLAXE NACH ELEKTIVEM HUFT- UND KNIEGELENKERSATZ.
AUTHOR: Mouret P.
CORPORATE SOURCE: P. Mouret, Orthopodische Klinik, Staedt. Klin. Frankfurt-Main/Hochst, Gotenstrasse 6.8, 65929 Frankfurt, Germany
SOURCE: Hamostaseologie, (2002) Vol. 22, No. 3, pp. 103-106.
Refs: 11
ISSN: 0720-9355 CODEN: HAEMD2
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 025 Hematology
030 Pharmacology
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English; German

ENTRY DATE: Entered STN: 20020919
Last Updated on STN: 20020919

AB Aim: The efficacy and safety of the new oral, direct and selective thrombin inhibitor Ximelagatran and its active form Melagatran was analysed in patients undergoing total hip or knee replacement. Methods and patients: Methro II, a randomised, double-blind controlled dose-finding study, involved 1876 patients. Melagatran (1, 1.5, 2.25 or 3 mg; twice daily; start: immediately before surgery) was given subcutaneously, followed by orally administered Ximelagatran (8, 12, 18 or 24 mg, twice daily, day after surgery) and compared to subcutaneously administered dalteparin (5000 IE, once daily). Methro III was a randomised, double blind controlled study involving 2788 patients. The fixed dose of 3 mg Melagatran was given (start: 4-12 hours postoperatively) followed by oral Ximelagatran (24 mg, twice daily, day after surgery) compared to subcutaneous enoxaparin (40 mg, once daily). In both studies, dalteparin or enoxaparin was applied at the evening before operation; the treatment lasted 8 to 11 days. A bilateral venography was performed at the last day of treatment. Results: In the Methro II study, 1270 patients underwent total hip, 606 total knee replacement. In both groups the thromboembolism rate was reduced depending on the dose of Ximelagatran/Melagatran. Compared to dalteparin, it was significantly lower for the Ximelagatran/Melagatran group with the highest dose. In the Methro III study 1923 patients underwent a total hip, 865 a total knee replacement. The thromboembolism rate was 31% for the Ximelagatran/Melagatran group compared to 27% for the enoxaparin group. In both studies blood loss and **transfusion** requirement were in the same range as with low weight molecular heparins. Conclusions: A fixed subcutaneously given dose of Melagatran, followed by orally administered Ximelagatran is effective and well tolerated as prophylaxis against venous thromboembolism.

AB . . . rate was 31% for the Ximelagatran/Melagatran group compared to 27% for the enoxaparin group. In both studies blood loss and **transfusion** requirement were in the same range as with low weight molecular heparins. Conclusions: A fixed subcutaneously given dose of Melagatran,. . .

RN (ximelagatran) 192939-46-1; (melagatran) **159776-70-2**; (enoxaparin) 9041-08-1

L2 ANSWER 18 OF 18 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002062086 EMBASE

TITLE: A dose-ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prophylaxis of thromboembolism after hip or knee replacement: METHRO I.

AUTHOR: Eriksson B.I.; Arfwidsson A.-C.; Frison L.; Eriksson U.G.; Bylock A.; Kalebo P.; Fager G.; Gustafsson D.

CORPORATE SOURCE: B.I. Eriksson, Department of Orthopaedic Surgery, Sahlgrenska Univ. Hospital Ostra, S-41685 Goteborg, Sweden. b.eriksson@orthop.gu.se

SOURCE: Thrombosis and Haemostasis, (2002) Vol. 87, No. 2, pp. 231-237.
Refs: 21
ISSN: 0340-6245 CODEN: THHADQ

COUNTRY: Germany

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
033 Orthopedic Surgery
038 Adverse Reactions Titles
025 Hematology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20020301

Last Updated on STN: 20020301

AB The novel, oral direct thrombin inhibitor, ximelagatran (formerly H 376/95), represents an advance in antithrombotic therapy through its oral availability. After oral administration, ximelagatran is converted to its active form, melagatran. Melagatran can also be administered subcutaneously (sc). The results from the first clinical study with ximelagatran are reported. In this randomized, parallel-group, controlled study, 103 patients scheduled for elective total hip or total knee replacement received sc melagatran (1, 2 or 4 mg bid) for 2 days commencing immediately before surgery, followed by oral ximelagatran (6, 12 or 24 mg bid) for 6-9 days. Another 33 patients received dalteparin 5000 IU sc once daily, started the evening before surgery, for 8-11 days. At bilateral venography, deep vein thrombosis was found in 20.5% (16/78) of patients who had received sc melagatran and oral ximelagatran and in 18.5% (5/27) of patients in the dalteparin group. The study did not evaluate a dose-response for efficacy, and no differences between the three dose levels of melagatran and ximelagatran were shown. No pulmonary embolism was diagnosed during treatment. Total bleeding in the sc melagatran plus oral ximelagatran groups showed no dose-response and was similar to that seen in the dalteparin group. The pharmacokinetic properties of melagatran in the surgery patients were consistent with those observed for healthy subjects, and the APTT ratio, which increased non-linearly with plasma melagatran concentration, showed a consistent concentration-effect relationship during the treatment period. Ximelagatran and melagatran were well tolerated. In conclusion, ximelagatran and its active form melagatran appear to be promising agents for the prevention of venous thromboembolism following orthopaedic surgery.

CT Medical Descriptors:
*deep . . . efficacy
lung embolism
postoperative hemorrhage: SI, side effect
postoperative hemorrhage: TH, therapy
partial thromboplastin time
drug blood level
drug tolerability
orthopedic surgery
drug safety
area under the curve
maximum allowable concentration
blood transfusion
hernia: SI, side effect
disease severity
article
priority journal
*thrombin inhibitor: DT, drug therapy
*thrombin inhibitor: CT, clinical trial
*thrombin inhibitor: PD, pharmacology
*thrombin inhibitor: DO,. . .

RN (ximelagatran) 192939-46-1; (melagatran) **159776-70-2**

=> d l3 1-9 ibib abs kwic

L3 ANSWER 1 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2002298505 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12031965
TITLE: Inhibition of thrombin abrogates the instant blood-mediated inflammatory reaction triggered by isolated human islets: possible application of the thrombin inhibitor melagatran in clinical islet **transplantation.**
AUTHOR: Ozmen Lisa; Ekdahl Kristina Nilsson; Elgue Graciela; Larsson Rolf; Korsgren Olle; Nilsson Bo
CORPORATE SOURCE: Department of Radiology, Oncology and Clinical Immunology, Division of Clinical Immunology, the Rudbeck Laboratory,

University Hospital, Uppsala, Sweden.
SOURCE: Diabetes, (2002 Jun) 51 (6) 1779-84.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020602
Last Updated on STN: 20020625
Entered Medline: 20020624

AB A thrombotic/inflammatory reaction is elicited when isolated islets of Langerhans come in contact with ABO-compatible blood. The detrimental effects of this instant blood-mediated inflammatory reaction (IBMIR) provide a reasonable explanation for the observation that an unexpectedly high number of islets, from several donors, are needed to produce normoglycemia in transplant patients with type 1 diabetes. In this study, the hypothesis that a specific thrombin inhibitor, Melagatran, could reduce IBMIR in an in vitro model in which human islets are exposed to ABO-compatible blood was tested. The administration of Melagatran abrogated IBMIR dose-dependently. Islets exposed to blood, in the absence or presence of 0.4 micromol/l Melagatran, exhibited a loss of integrity and were found to be trapped in macroscopic clots containing platelets and CD11b(+) leukocytes. At concentrations from 1 to 10 micromol/l, Melagatran inhibited both coagulation and complement activation. Also, platelet and leukocyte activation and consumption were decreased. Islet morphology was maintained with almost no platelets adhering to the surface, and infiltration by CD11b(+) leukocytes was considerably reduced. In conclusion, Melagatran significantly reduced IBMIR in this model system. This protective effect indicates that thrombin plays a pivotal role in IBMIR and suggests that thrombin inhibition can improve the outcome of clinical islet **transplantation.**

TI . . . the instant blood-mediated inflammatory reaction triggered by isolated human islets: possible application of the thrombin inhibitor melagatran in clinical islet **transplantation.**

AB . . . that thrombin plays a pivotal role in IBMIR and suggests that thrombin inhibition can improve the outcome of clinical islet **transplantation.**

CT . . .
therapeutic use
Humans
Immunohistochemistry
*Inflammation: BL, blood
Inflammation: PA, pathology
*Inflammation: PC, prevention & control
*Islets of Langerhans: PP, physiopathology
***Islets of Langerhans Transplantation**
Middle Aged
Neutrophils: PA, pathology
Platelet Glycoprotein GPIIb-IIIa Complex: AN, analysis
Research Support, Non-U.S. Gov't
*Thrombin: AI,. . .
RN **159776-70-2 (melagatran)**; 56-40-6 (Glycine); 9001-31-4 (Fibrin)

L3 ANSWER 2 OF 9 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:380473 BIOSIS
DOCUMENT NUMBER: PREV200200380473
TITLE: Inhibition of thrombin abrogates the instant blood-mediated inflammatory reaction triggered by isolated human islets: Possible application of the thrombin inhibitor Melagatran in clinical islet **transplantation.**
AUTHOR(S): Ozmen, Lisa; Ekdahl, Kristina Nilsson; Elgue, Graciela; Larsson, Rolf; Korsgren, Olle; Nilsson, Bo [Reprint author]
CORPORATE SOURCE: Department of Radiology, Oncology and Clinical Immunology, Division of Clinical Immunology, Rudbeck Laboratory,

University Hospital, S-75185, Uppsala, Sweden
bo.nilsson@klinimm.uu.se
SOURCE: Diabetes, (June, 2002) Vol. 51, No. 6, pp. 1779-1784. print.
CODEN: DIAEAZ. ISSN: 0012-1797.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Jul 2002
Last Updated on STN: 10 Jul 2002

AB A thrombotic/inflammatory reaction is elicited when isolated islets of Langerhans come in contact with ABO-compatible blood. The detrimental effects of this instant blood-mediated inflammatory reaction (IBMIR) provide a reasonable explanation for the observation that an unexpectedly high number of islets, from several donors, are needed to produce normoglycemia in transplant patients with type 1 diabetes. In this study, the hypothesis that a specific thrombin inhibitor, Melagatran, could reduce IBMIR in an in vitro model in which human islets are exposed to ABO-compatible blood was tested. The administration of Melagatran abrogated IBMIR dose-dependently. Islets exposed to blood, in the absence or presence of 0.4 mumol/l Melagatran, exhibited a loss of integrity and were found to be trapped in macroscopic clots containing platelets and CD11b+ leukocytes. At concentrations from 1 to 10 mumol/l, Melagatran inhibited both coagulation and complement activation. Also, platelet and leukocyte activation and consumption were decreased. Islet morphology was maintained with almost no platelets adhering to the surface, and infiltration by CD11b+ leukocytes was considerably reduced. In conclusion, Melagatran significantly reduced IBMIR in this model system. This protective effect indicates that thrombin plays a pivotal role in IBMIR and suggests that thrombin inhibition can improve the outcome of clinical islet **transplantation.**

TI . . . the instant blood-mediated inflammatory reaction triggered by isolated human islets: Possible application of the thrombin inhibitor Melagatran in clinical islet **transplantation.**

AB . . . that thrombin plays a pivotal role in IBMIR and suggests that thrombin inhibition can improve the outcome of clinical islet **transplantation.**

RN **159776-70-2** (melagatran)
9002-04-4 (thrombin)

L3 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:591023 CAPLUS
DOCUMENT NUMBER: 139:128039
TITLE: The use of melagatran for the manufacture of a medicament for the treatment of type 1 diabetes mellitus
INVENTOR(S): Korsgren, Olle; Nilsson, Bo
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003061682	A1	20030731	WO 2003-SE87	20030121

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2472241	AA	20030731	CA 2003-2472241	20030121
EP 1469874	A1	20041027	EP 2003-701203	20030121
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003006798	A	20041207	BR 2003-6798	20030121
US 2005090424	A1	20050428	US 2003-502069	20030121
JP 2005516035	T2	20050602	JP 2003-561625	20030121
PRIORITY APPLN. INFO.:			SE 2002-198 A	20020123
			WO 2003-SE87 W	20030121

AB According to the invention there is provided the use of melagatran, or a pharmaceutically-acceptable derivative thereof, for the manufacture of a medicament for the treatment of Type I diabetes and for the manufacture of a medicament for use in a method of **transplantation** of cells, including insulin-producing cells, such as islets of Langerhans or stem cells. Melagatran and derivs. thereof enhance the engraftment of islets of Langerhans in the liver following **transplantation**, when compared to engraftment following **transplantation** in the absence of melagatran.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB According to the invention there is provided the use of melagatran, or a pharmaceutically-acceptable derivative thereof, for the manufacture of a medicament for the treatment of Type I diabetes and for the manufacture of a medicament for use in a method of **transplantation** of cells, including insulin-producing cells, such as islets of Langerhans or stem cells. Melagatran and derivs. thereof enhance the engraftment of islets of Langerhans in the liver following **transplantation**, when compared to engraftment following **transplantation** in the absence of melagatran.

ST diabetes melagatran Langerhans islet **transplantation**

IT Liver
(Langerhans islets engraftment in; melagatran for treatment of type 1 diabetes and for cell **transplantation**)

IT Autoimmune disease
(insulin-dependent diabetes mellitus; melagatran for treatment of type 1 diabetes and for cell **transplantation**)

IT Diabetes mellitus
(insulin-dependent; melagatran for treatment of type 1 diabetes and for cell **transplantation**)

IT Stem cell
(melagatran for treatment of type 1 diabetes and for cell **transplantation**)

IT Transplant and **Transplantation**
(pancreatic islet; melagatran for treatment of type 1 diabetes and for cell **transplantation**)

IT Liver
(toxicity, Langerhans islets engraftment in; melagatran for treatment of type 1 diabetes and for cell **transplantation**)

IT Pancreatic islet of Langerhans
(transplant; melagatran for treatment of type 1 diabetes and for cell **transplantation**)

IT **159776-70-2**, Melagatran
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(melagatran for treatment of type 1 diabetes and for cell **transplantation**)

L3 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:430760 CAPLUS
DOCUMENT NUMBER: 137:332856
TITLE: Inhibition of thrombin abrogates the instant

blood-mediated inflammatory reaction triggered by isolated human islets: possible application of the thrombin inhibitor melagatran in clinical islet **transplantation**

AUTHOR(S): Ozmen, Lisa; Ekdahl, Kristina Nilsson; Elgue, Graciela; Larsson, Rolf; Korsgren, Olle; Nilsson, Bo

CORPORATE SOURCE: Department of Radiology, Oncology and Clinical Immunology, Division of Clinical Immunology, the Rudbeck Laboratory, University Hospital, Uppsala, S-75185, Swed.

SOURCE: Diabetes (2002), 51(6), 1779-1784
CODEN: DIAEAZ; ISSN: 0012-1797

PUBLISHER: American Diabetes Association

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A thrombotic/inflammatory reaction is elicited when isolated islets of Langerhans come in contact with ABO-compatible blood. The detrimental effects of this instant blood-mediated inflammatory reaction (IBMIR) provide a reasonable explanation for the observation that an unexpectedly high number of islets, from several donors, are needed to produce normoglycemia in transplant patients with type 1 diabetes. In this study, the hypothesis that a specific thrombin inhibitor, Melagatran, could reduce IBMIR in an in vitro model in which human islets are exposed to ABO-compatible blood was tested. The administration of Melagatran abrogated IBMIR dose-dependently. Islets exposed to blood, in the absence or presence of 0.4 μmol/l Melagatran, exhibited a loss of integrity and were found to be trapped in macroscopic clots containing platelets and CD11b+ leukocytes. At concns. from 1 to 10 μmol/l, Melagatran inhibited both coagulation and complement activation. Also, platelet and leukocyte activation and consumption were decreased. Islet morphol. was maintained with almost no platelets adhering to the surface, and infiltration by CD11b+ leukocytes was considerably reduced. In conclusion, Melagatran significantly reduced IBMIR in this model system. This protective effect indicates that thrombin plays a pivotal role in IBMIR and suggests that thrombin inhibition can improve the outcome of clin. islet **transplantation.**

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Inhibition of thrombin abrogates the instant blood-mediated inflammatory reaction triggered by isolated human islets: possible application of the thrombin inhibitor melagatran in clinical islet **transplantation**

AB A thrombotic/inflammatory reaction is elicited when isolated islets of Langerhans come in contact with ABO-compatible blood. The detrimental effects of this instant blood-mediated inflammatory reaction (IBMIR) provide a reasonable explanation for the observation that an unexpectedly high number of islets, from several donors, are needed to produce normoglycemia in transplant patients with type 1 diabetes. In this study, the hypothesis that a specific thrombin inhibitor, Melagatran, could reduce IBMIR in an in vitro model in which human islets are exposed to ABO-compatible blood was tested. The administration of Melagatran abrogated IBMIR dose-dependently. Islets exposed to blood, in the absence or presence of 0.4 μmol/l Melagatran, exhibited a loss of integrity and were found to be trapped in macroscopic clots containing platelets and CD11b+ leukocytes. At concns. from 1 to 10 μmol/l, Melagatran inhibited both coagulation and complement activation. Also, platelet and leukocyte activation and consumption were decreased. Islet morphol. was maintained with almost no platelets adhering to the surface, and infiltration by CD11b+ leukocytes was considerably reduced. In conclusion, Melagatran significantly reduced IBMIR in this model system. This protective effect indicates that thrombin plays a pivotal role in IBMIR and suggests that thrombin inhibition can improve the outcome of clin. islet **transplantation.**

ST thrombin inhibitor melagatran blood mediated inflammation islet **transplantation**

IT CD antigens

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD11B, leukocytes; thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

IT Leukocyte
(CD11b+; thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

IT Inflammation
(blood-mediated; thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

IT Autoimmune disease
(insulin-dependent diabetes mellitus; thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

IT Diabetes mellitus
(insulin-dependent; thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

IT Transplant and **Transplantation**
(pancreas, islet; thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

IT Anti-inflammatory agents
Cytoprotective agents
Human
Pancreatic islet of Langerhans
Platelet (blood)
(thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

IT Pancreas
(transplant, islet; thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αM, leukocytes; thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

IT 9002-04-4, Thrombin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

IT **159776-70-2**, Melagatran
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet **transplantation**)

L3 ANSWER 5 OF 9 EMBASE on STN

ACCESSION NUMBER: 2004517046 EMBASE
TITLE: Blasts from the past.
AUTHOR: Insel P.A.; Kornfeld S.; Majerus P.W.; Marks A.R.; Marks P.A.; Relman A.S.; Scharschmidt B.F.; Stossel T.P.; Varki A.P.; Weiss S.J.; Wilson J.D.
CORPORATE SOURCE: P.A. Insel, 630 West 168th Street, New York, NY 10032, United States. editors@the-jci.org
SOURCE: Journal of Clinical Investigation, (2004) Vol. 114, No. 8, pp. 1017-1033.
Refs: 114
ISSN: 0021-9738 CODEN: JCINAO

COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20041228
Last Updated on STN: 20041228

AB With this issue of the JCI, we celebrate the 80th anniversary of the Journal. While 80 years is not a century, we still feel it is important to honor what the JCI has meant to the biomedical research community for 8 decades. To illustrate why the JCI is the leading general-interest translational research journal edited by and for biomedical researchers, we have asked former JCI editors-in-chief to reflect on some of the major scientific advances reported in the pages of the Journal during their tenures.

CT Medical Descriptors:
*medical . . . PC, prevention
inflammatory disease
phagocytosis
pneumonia: DT, drug therapy
juvenile rheumatoid arthritis: DT, drug therapy
tumor vascularization
Tangier disease: ET, etiology
drug safety
enteritis
preeclampsia
pancreas cancer: DT, drug therapy
pancreas cell
stem cell transplantation
diabetes mellitus: DT, drug therapy
diabetes mellitus: TH, therapy
human
nonhuman
clinical trial
review
priority journal
alteplase: CT, clinical trial
alteplase: DT, drug therapy
alteplase: PD, pharmacology
glucagon:. . .

RN. . . 139639-24-0; (streptokinase) 9002-01-1; (enalapril) 75847-73-3; (interleukin 8) 114308-91-7; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (hirudin) 8001-27-2; (argatroban) 74863-84-6; (hirulog) 128270-60-0; (melagatran) **159776-70-2**; (ximelagatran) 192939-46-1, 260790-58-7; (metformin) 1115-70-4, 657-24-9; (imatinib) 152459-95-5, 220127-57-1; (bevacizumab) 216974-75-3; (semaxanib) 186610-95-7; (2,4 dimethyl 5 (2 oxo 1h indol. . .

L3 ANSWER 6 OF 9 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004510055 EMBASE
TITLE: Protecting pancreatic β-cells.
AUTHOR: Pileggi A.; Fenjves E.S.; Klein D.; Ricordi C.; Pastori R.L.
CORPORATE SOURCE: Dr. R.L. Pastori, Diabetes Research Institute, Univ. of Miami School of Medicine, 1450 NW 10th Avenue, Miami, FL 33136, United States. rpastori@med.miami.edu
SOURCE: IUBMB Life, (2004) Vol. 56, No. 7, pp. 387-394.
Refs: 70
ISSN: 1521-6543 CODEN: IULIF8
COUNTRY: United States

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20041217
Last Updated on STN: 20041217

AB Type 1 diabetes mellitus is an autoimmune disorder in which the insulin-producing β-cells of the pancreatic islets of Langerhans are selectively destroyed. **Transplantation** of allogeneic islets offers a novel therapeutic approach for type 1 diabetic patients. Primary obstacles to the successful outcome of this treatment are loss of the islets occurring first during the isolation procedure and then immediately following **transplantation.** The genetic make up of β-cells contributes to making them particularly vulnerable to apoptosis and necrosis-induced cell death caused by the trauma of the isolation procedure and by non-specific inflammatory events at the **transplantation** site. In this review we present description of chemical and molecular biology based strategies to confer cytoprotection to β-cells.

AB . . . diabetes mellitus is an autoimmune disorder in which the insulin-producing β-cells of the pancreatic islets of Langerhans are selectively destroyed. **Transplantation** of allogeneic islets offers a novel therapeutic approach for type 1 diabetic patients. Primary obstacles to the successful outcome of this treatment are loss of the islets occurring first during the isolation procedure and then immediately following **transplantation.** The genetic make up of β-cells contributes to making them particularly vulnerable to apoptosis and necrosis-induced cell death caused by the trauma of the isolation procedure and by non-specific inflammatory events at the **transplantation** site. In this review we present description of chemical and molecular biology based strategies to confer cytoprotection to β-cells.

CT Medical Descriptors:
*pancreas islet beta cell
*cell protection
insulin dependent diabetes mellitus
autoimmune disease
insulin release
pancreas islet
allogeneic hematopoietic stem cell transplantation
treatment outcome
isolation procedure
genetic analysis
apoptosis
cell death
inflammation
binding site
chemical analysis
molecular biology
gene therapy
gene vector
human
controlled study
human cell
review
calcitriol
estradiol
carbon monoxide
cyclooxygenase 2 inhibitor
glucagon like. . .

RN. . . 66772-14-3; (estradiol) 50-28-2; (carbon monoxide) 630-08-0; (glucagon like peptide) 82905-30-4; (lisofylline) 100324-81-0, 151852-32-3, 6493-06-7; (dextran) 87915-38-6, 9014-78-2; (protoporphyrin) 553-12-8; (melagatran) **159776-70-2**; (nicotinamide) 11032-50-1,

98-92-0; (pyruvic acid) 127-17-3, 19071-34-2, 57-60-3; (proteinase inhibitor) 37205-61-1; (superoxide dismutase) 37294-21-6, 9016-01-7, 9054-89-1; (scatter factor) 67256-21-7, 72980-71-3

L3 ANSWER 7 OF 9 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004054041 EMBASE
TITLE: [The Best of Clinical Pharmacology in 2003]. L'ESSENTIEL DE 2003 EN PHARMACOLOGIE CLINIQUE CARDIOVASCULAIRE.
AUTHOR: Ambrosi P.; Gayet J.-L.; Andrejak M.
CORPORATE SOURCE: France. pambrosi@ap-hm.fr
SOURCE: Archives des Maladies du Coeur et des Vaisseaux, (2004) Vol. 97, No. SPEC. ISS. 1, pp. 41-46.
Refs: 34
ISSN: 0003-9683 CODEN: AMCVAN
COUNTRY: France
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: French
SUMMARY LANGUAGE: English; French
ENTRY DATE: Entered STN: 20040220
Last Updated on STN: 20040220

AB Again it is the development of renin-angiotensin-aldosterone system inhibitors which has brought the most novel information during the year 2003. The arrival on the market of eplerenone represents a veritable advance because this anti-aldosterone shares the properties of spironolactone in hypertension and cardiac failure without provoking either gynaecomastia or dysmenorrhoea. The significance of the sartans in hypertension has been confirmed. They occupy a position as second line medication in cardiac failure, indicated either in association with ACE inhibitors or in place of ACE inhibitors when they cause a cough, as the CHARM study has shown. Some new properties have been attributed to them by recent trials: prevention of migraine, prevention of AF after cardioversion and improvement of the prognosis when they are administered in the acute phase of ischaemic CVA. Concerning ACE inhibitors, the ALLHAT study has answered an old yet until now unresolved question by comparing side by side an ACE inhibitor with a diuretic in hypertension. The ACE inhibitor prevented coronary events just as well as the diuretic, but slightly less well for ischaemic CVA. In stable coronary patients with no cardiac failure, the EUROPA study confirms the preventive role of an ACE inhibitor. In the area of atherosclerosis prevention, the statins again occupy centre stage. Their place in primary prevention in hypertensives, diabetics and renal transplant patients has been studied specifically. It emerges that within these populations, the benefit is only clear in subjects with the highest level of risk. The significance of the statins for primary prevention in subjects aged over 70 years remains to be proven. Furthermore, the initial results of studies in progress to evaluate folates in the prevention of vascular events in atherosclerotic subjects have been published and are disappointing, but these studies lack power. In diabetics, recent trials suggest that certain new oral hypoglycaemics (α-glucosidase inhibitors) can prevent cardiovascular events. The two principal new anti-thrombotics, ximelagatran and fondaparinux, have proved their effectiveness in the prevention and treatment of venous thrombosis, as has melagatran for the prevention of thrombo-embolic accidents with AF and post-infarct. Their tolerance remains debatable, particularly after the description of elevated transaminases rather frequently with melagatran. Finally, the results of the BRAVO study confirm the poor risk/benefit ratio for oral anti-GPIIbIIIa.

CT Medical Descriptors:
*clinical . . . atrium fibrillation

cardioversion
prognosis
acute disease
heart muscle ischemia: DT, drug therapy
heart muscle ischemia: PC, prevention
atherosclerosis: DT, drug therapy
atherosclerosis: PC, prevention
diabetes mellitus: DT, drug therapy
kidney transplantation
high risk patient
vascular disease: DT, drug therapy
vascular disease: PC, prevention
drug efficacy
vein thrombosis: DT, drug therapy
vein thrombosis: PC, prevention
thromboembolism: DT, drug. . .

RN (spironolactone) 52-01-7; (ximelagatran) 192939-46-1, 260790-58-7; (fondaparinux) 104993-28-4, 114870-03-0; (melagatran) **159776-70-2** ; (aminotransferase) 9031-66-7; (eplerenone) 107724-20-9; (losartan) 114798-26-4; (candesartan) 139481-59-7; (irbesartan) 138402-11-6; (valsartan) 137862-53-4; (lisinopril) 76547-98-3, 83915-83-7; (enalapril) 75847-73-3; (perindopril) 82834-16-0; (atorvastatin). . .

L3 ANSWER 8 OF 9 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003249349 EMBASE
TITLE: Islet cell **transplantation** as a cure for insulin dependent diabetes: Current improvements in preserving islet cell mass and function.
AUTHOR: Fontaine M.J.; Fan W.
CORPORATE SOURCE: Dr. M.J. Fontaine, Department of Pathology, Medical University of South Carolina, 165 Ashley Ave., Charleston, SC 29425, United States. fontainm@musc.edu
SOURCE: Hepatobiliary and Pancreatic Diseases International, (2003) Vol. 2, No. 2, pp. 170-179.
Refs: 72
ISSN: 1499-3872 CODEN: HPDIAJ
COUNTRY: China
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
009 Surgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030710
Last Updated on STN: 20030710

AB Objective: To review the current progress of islet cell **transplantation** in patients with insulin-dependent diabetes, emphasizing on the difficulties with recovering and preserving islet cell mass and function, 30% of which is lost during the peri-**transplantation** period. Results: The islet-cell isolation technique is perfected, but improvements are still progressing in two major directions: preservation of islet cells and tolerance induction. Optimum islet cell viability and function depends on appropriate revascularization of the islet graft and blockade of thrombus formation as well as cytokine and free radical release. Conditioning the islet cells in-vitro prior to **transplantation** to either upregulate VEGF expression or downregulate NF-kappa B transcription factor has proven to improve revascularization and to prevent islet cell apoptosis and cytokine-mediated damage. Tolerance induction is currently being best achieved by selecting and combining immunosuppressive agents such as monoclonal antibodies which target the major signaling molecules during

immune activation, but which are least toxic to islet cells. Conclusions: Patients with insulin-dependent diabetes will greatly benefit from current developments in effective approaches to protect islets during the peritransplant period. Emerging interest in stem cell biology and differentiation may provide the ultimate solution to the problem of organ scarcity and islet cell protection from the peritransplant induced damage.

TI Islet cell **transplantation** as a cure for insulin dependent diabetes: Current improvements in preserving islet cell mass and function.

AB Objective: To review the current progress of islet cell **transplantation** in patients with insulin-dependent diabetes, emphasizing on the difficulties with recovering and preserving islet cell mass and function, 30% of which is lost during the peri-**transplantation** period. Results: The islet-cell isolation technique is perfected, but improvements are still progressing in two major directions: preservation of islet. . . and blockade of thrombus formation as well as cytokine and free radical release. Conditioning the islet cells in-vitro prior to **transplantation** to either upregulate VEGF expression or downregulate NF-kappa B transcription factor has proven to improve revascularization and to prevent islet. . .

CT Medical Descriptors:

*insulin dependent diabetes mellitus: SU, surgery
***pancreas islet transplantation**
*graft preservation
treatment indication
pancreas islet cell
pancreas islet cell function
perioperative period
cell loss
cell isolation
isolation procedure
immunological tolerance
cell viability
revascularization
vein thrombosis: CO, complication
vein thrombosis: DT, drug therapy
vein thrombosis: PC, prevention
cytokine release
preoperative period
upregulation
protein expression
down regulation
treatment outcome
apoptosis
cell damage
immunosuppressive treatment
drug targeting
signal transduction
immune response
cytotoxicity
cell protection
stem cell
cell differentiation
organ transplantation
graft rejection: CO, complication
graft rejection: DT, drug therapy
graft rejection: PC, prevention
drug potentiation
diabetogenesis
diabetes mellitus: SI, side effect
diabetes mellitus: SU, surgery
human
nonhuman
mouse
review
free. . .

RN (vasculotropin) 127464-60-2; (interleukin 2 receptor antibody) 179045-86-4; (tsukubaenolide) 104987-11-3; (rapamycin) 53123-88-9; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (melagatran) **159776-70-2**; (tissue factor pathway inhibitor) 116638-34-7; (gamma interferon) 82115-62-6; (cyclosporin A) 59865-13-3, 63798-73-2; (nicotinamide) 11032-50-1, 98-92-0; (nitric oxide) 10102-43-9; (aminoguanidine) 1068-42-4,. . .

L3 ANSWER 9 OF 9 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002191339 EMBASE

TITLE: Inhibition of thrombin abrogates the instant blood-mediated inflammatory reaction triggered by isolated human islets: Possible application of the thrombin inhibitor Melagatran in clinical islet **transplantation.**

AUTHOR: Ozmen L.; Ekdahl K.N.; Elgue G.; Larsson R.; Korsgren O.; Nilsson B.

CORPORATE SOURCE: Dr. B. Nilsson, Department of Radiology, Rudbeck Laboratory, University Hospital, S-75185 Uppsala, Sweden. bo.nilsson@klinimm.uu.se

SOURCE: Diabetes, (2002) Vol. 51, No. 6, pp. 1779-1784.
Refs: 32
ISSN: 0012-1797 CODEN: DIAEAZ

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology
026 Immunology, Serology and Transplantation
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20020620
Last Updated on STN: 20020620

AB A thrombotic/inflammatory reaction is elicited when isolated islets of Langerhans come in contact with ABO-compatible blood. The detrimental effects of this instant blood-mediated inflammatory reaction (IBMIR) provide a reasonable explanation for the observation that an unexpectedly high number of islets, from several donors, are needed to produce normoglycemia in transplant patients with type 1 diabetes. In this study, the hypothesis that a specific thrombin inhibitor, Melagatran, could reduce IBMIR in an in vitro model in which human islets are exposed to ABO-compatible blood was tested. The administration of Melagatran abrogated IBMIR dose-dependently. Islets exposed to blood, in the absence or presence of 0.4 μmol/l Melagatran, exhibited a loss of integrity and were found to be trapped in macroscopic clots containing platelets and CD11b(+) leukocytes. At concentrations from 1 to 10 μmol/l, Melagatran inhibited both coagulation and complement activation. Also, platelet and leukocyte activation and consumption were decreased. Islet morphology was maintained with almost no platelets adhering to the surface, and infiltration by CD11b(+) leukocytes was considerably reduced. In conclusion, Melagatran significantly reduced IBMIR in this model system. This protective effect indicates that thrombin plays a pivotal role in IBMIR and suggests that thrombin inhibition can improve the outcome of clinical islet **transplantation.**

TI . . . the instant blood-mediated inflammatory reaction triggered by isolated human islets: Possible application of the thrombin inhibitor Melagatran in clinical islet **transplantation.**

AB . . . that thrombin plays a pivotal role in IBMIR and suggests that thrombin inhibition can improve the outcome of clinical islet **transplantation.**

CT Medical Descriptors:
*inflammation
***pancreas islet transplantation**
insulin dependent diabetes mellitus: SU, surgery
disease model
dose response

blood clotting
complement activation
cell structure
neutrophil chemotaxis
treatment outcome
enzyme immunoassay
immunohistochemistry
blood group ABO incompatibility
human
controlled study
human cell
article
priority. . .

RN (melagatran) **159776-70-2**; (thrombin) 9002-04-4

=> d l4 1-2 ibib abs kwic

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:591023 CAPLUS
DOCUMENT NUMBER: 139:128039
TITLE: The use of melagatran for the manufacture of a medicament for the treatment of type 1 diabetes mellitus
INVENTOR(S): Korsgren, Olle; Nilsson, Bo
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003061682	A1	20030731	WO 2003-SE87	20030121
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2472241	AA	20030731	CA 2003-2472241	20030121
EP 1469874	A1	20041027	EP 2003-701203	20030121
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003006798	A	20041207	BR 2003-6798	20030121
US 2005090424	A1	20050428	US 2003-502069	20030121
JP 2005516035	T2	20050602	JP 2003-561625	20030121
PRIORITY APPLN. INFO.:			SE 2002-198 A	20020123
			WO 2003-SE87 W	20030121

AB According to the invention there is provided the use of melagatran, or a pharmaceutically-acceptable derivative thereof, for the manufacture of a medicament for the treatment of Type I diabetes and for the manufacture of a medicament for use in a method of transplantation of cells, including insulin-producing cells, such as islets of Langerhans or stem cells. Melagatran and derivs. thereof enhance the engraftment of islets of Langerhans in the liver following transplantation, when compared to engraftment following transplantation in the absence of melagatran.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Pancreatic **islet** of **Langerhans**
(transplant; melagatran for treatment of type 1 diabetes and for cell transplantation)

IT **159776-70-2**, Melagatran
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(melagatran for treatment of type 1 diabetes and for cell transplantation)

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:430760 CAPLUS
DOCUMENT NUMBER: 137:332856
TITLE: Inhibition of thrombin abrogates the instant blood-mediated inflammatory reaction triggered by isolated human islets: possible application of the thrombin inhibitor melagatran in clinical islet transplantation
AUTHOR(S): Ozmen, Lisa; Ekdahl, Kristina Nilsson; Elgue, Graciela; Larsson, Rolf; Korsgren, Olle; Nilsson, Bo
CORPORATE SOURCE: Department of Radiology, Oncology and Clinical Immunology, Division of Clinical Immunology, the Rudbeck Laboratory, University Hospital, Uppsala, S-75185, Swed.
SOURCE: Diabetes (2002), 51(6), 1779-1784
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A thrombotic/inflammatory reaction is elicited when isolated islets of Langerhans come in contact with ABO-compatible blood. The detrimental effects of this instant blood-mediated inflammatory reaction (IBMIR) provide a reasonable explanation for the observation that an unexpectedly high number of islets, from several donors, are needed to produce normoglycemia in transplant patients with type 1 diabetes. In this study, the hypothesis that a specific thrombin inhibitor, Melagatran, could reduce IBMIR in an in vitro model in which human islets are exposed to ABO-compatible blood was tested. The administration of Melagatran abrogated IBMIR dose-dependently. Islets exposed to blood, in the absence or presence of 0.4 μmol/l Melagatran, exhibited a loss of integrity and were found to be trapped in macroscopic clots containing platelets and CD11b+ leukocytes. At concns. from 1 to 10 μmol/l, Melagatran inhibited both coagulation and complement activation. Also, platelet and leukocyte activation and consumption were decreased. Islet morphol. was maintained with almost no platelets adhering to the surface, and infiltration by CD11b+ leukocytes was considerably reduced. In conclusion, Melagatran significantly reduced IBMIR in this model system. This protective effect indicates that thrombin plays a pivotal role in IBMIR and suggests that thrombin inhibition can improve the outcome of clin. islet transplantation.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Anti-inflammatory agents
Cytoprotective agents
Human
Pancreatic **islet** of **Langerhans**
Platelet (blood)
(thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet transplantation)

IT **159776-70-2**, Melagatran
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thrombin inhibition abrogates instant blood-mediated inflammatory reaction triggered by human islets: implication for melagatran use in islet transplantation)

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=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    94.13      94.34

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -5.11      -5.11

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